Clinical factors impacting quality of life and outcomes through the transition from pre-dialysis chronic kidney disease to early dialysis treatment

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Chapter 1

General introduction

General introduction

1. End Stage Renal Disease in the United States

Chronic Kidney Disease (CKD) is a common disease not only in the United States (U.S.), but also around the world in both developed and developing countries.[1,2] CKD meets the following criteria for a public health crisis:[3]

- High disease burden affecting many people with disease rates expected to increase worldwide
- Minority and socioeconomically deprived individuals are disproportionately impacted
- Interventions early in the disease process that may be political, economic, environmental, or clinical may change the course of the disease
- There are known disease prevention and mitigation strategies that are not yet in place and there is opportunity to determine new, meaningful interventions.

An estimated 30 million American adults, 15% of the adult U.S. population, have CKD as defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) guidelines of having an abnormal estimated glomerular filtration rate (eGFR) and/or urine albumin loss (albuminuria) for at least 3 months.[4,5] CKD has a severity continuum from mild to severe disease. Laboratory values of eGFR and albuminuria allow diagnosis of CKD stages from mild CKD stage 1 to CKD stage 5D or End Stage Renal Disease (ESRD). ESRD is a fatal disease without renal replacement therapy (RRT) from dialysis or renal transplant.

The 2017 United States Renal Data System (USRDS) Annual Data Report (ADR) documents 124,114 new patients starting RRT in the U.S. including 108,826 (87.7%) starting hemodialysis (HD), 11,864 (9.6%) starting peritoneal dialysis (PD), and 3,142 (2.5%) receiving a primary renal transplant before starting dialysis.[6] ESRD incidence rates have declined since 2006 due to improvements in treatment to slow progression of CKD. During this time the number of prevalent patients on dialysis has risen consistent with successful efforts to reduce mortality for dialysis patients. Current USRDS data reports 703,243 prevalent ESRD patients including 437,527 (63.3%) on HD, 48,770 (7.1%) on PD, and 202,810 (29.4%) with a renal transplant.[6]

2. Chronic dialysis treatment

Chronic dialysis treatment began in the U.S. on March 9, 1960 in Seattle, Washington with the first use of the Scribner Shunt to dialyze Clyde Shields.[7] Prior to the Scribner Shunt, HD using a semi-permeable artificial membrane was restricted to treatment for acute kidney injury.[8] Chronic HD requires longitudinal blood stream access which was limited until the development of the implantable Teflon coated Scribner Shunt. Initially chronic HD was performed in the hospital setting with very long dialysis treatments

once or twice per week.[7] Empirical observations, formal clinical research, political interests, technological advances, and health care funding have shaped current chronic HD programs to thrice weekly treatments in an outpatient facility staffed with a multi-disciplinary clinical team, although a minority of HD patients is treated in a home setting.[7,9]

In 1960 hospital-based chronic HD provided limited access to care necessitating treatment rationing.[7,10] To improve access to care, techniques were developed enabling patients to dialyze at home. Early home dialysis involved installing an HD machine in the home and supporting patients and care givers in managing and delivering an HD treatment. In the mid-1960s Fred Boen and Henry Tenckhoff developed a chronically indwelling PD catheter and an automatic cycler enabling home PD.[7,11] PD utilizes the natural semi-permeable membrane properties of the peritoneal cavity lining and peritoneal dialysate is infused either manually or with mechanical assistance into the peritoneal cavity. Fluid dwells in the peritoneum allowing diffusion and convection of small molecules into the dialysate.[12] Molecules and water are excreted with the PD dialysis fluid drain and dialysis continues as new fluid inflows into the peritoneal cavity. Compared to HD patients PD patients experience differences in some clinical parameters such as albumin (Alb) due to characteristics of the peritoneal membrane compared to synthetic HD dialyzer membranes.[13]

3. Dialysis treatment characteristics

Optimal care of late stage CKD patients includes education about dialysis treatment modalities which empowers patients to participate in treatment choices.[14-16] HD and PD have technical and psychosocial attributes that influence patient modality choice and patient quality of life (QOL).[17]

Qualitative research elucidates patient perceptions of modality characteristics which may favor HD or PD. PD treatment provides flexible schedules and slow, continuous treatment in a home setting. Patients who choose PD typically value freedom of schedule for work and travel and the convenience of a home-based treatment that does not require commuting to a treatment center.[17] Patients describe PD burdens including having supplies and dialysis equipment in the home and social isolation from other patients.[17] Both HD and PD have treatment risks which for PD includes peritonitis, an infection in the peritoneal cavity, which is painful and may adversely impact the opportunity to continue PD therapy.

Incenter HD involves trained, multi-disciplinary staff providing care which makes treatment seem more simple and secure for some patients.[17] Negative aspects of incenter HD include the inconvenience of traveling to an incenter location, dialysis schedules that are facility-centered, and the need for vascular access to the blood stream.[17] HD risks include vascular access complications, blood stream infections, and hemodynamic instability during HD treatments.

For both HD and PD routine monthly lab studies are done to assess anemia, bone and mineral metabolism (BMM), nutrition, and inflammation. Typical lab studies include hemoglobin (Hgb), serum calcium (Ca), serum phosphorus (Phos), Alb, and white blood cell (WBC) counts. In addition, clinical parameters such as body weight (Wt) and blood pressure (BP) are monitored before, during, and after every dialysis treatment. Lab results and clinical parameters provide objective assessments for clinical stability on PD and HD.

Previous research has defined treatment parameters associated with adverse dialysis outcomes for HD and PD including evidence of persistent volume overload, ongoing inflammation, cardiovascular (CV) instability, and abnormalities of BMM.[18-22] Fluid overload in ESRD is associated with cardiovascular complications including left ventricular hypertrophy and hypertension (HTN).[20] It is also associated with malnutrition, atherosclerosis, and inflammation and, as such, is a dialysis mortality risk factor.[20,22] Low BP and BP variability have been shown to adversely impact dialysis outcomes in the first year.[20] Changes in nutritional status and Wt in the incident dialysis period are associated with increased mortality.[21] Likewise, BMM parameters of Ca and Phos are associated with ESRD mortality probably through complications of atherosclerosis.[20,23,24]

While providing clinically safe and effective dialysis treatment is paramount, patient QOL while receiving this chronic treatment is also a key treatment goal. Patient QOL is measured routinely through use of the Kidney Disease Quality of Life – Short Form (KDQOL-SF) survey administered within the first 90 days of dialysis start and annually thereafter. The survey tool supports patient reported outcomes as a dialysis quality measure.[25]

4. Early dialysis mortality

Incident period HD defined as the first 90-120 days of dialysis treatment is associated with the highest mortality.[18,20,26] In 2007 the Dialysis Outcomes and Practice Patterns Study (DOPPS) group reported that for a U.S. cohort the first 120 days of HD had the highest mortality risk.[27] Chan, et.al. confirmed the highest risk of death in the first 90 days with a peak in mortality risk at week 2 for a cohort of over 300,000 patients starting HD in U.S. facilities operated by Fresenius Medical Care North America (FMCNA).[18] Factors associated with incident period HD mortality include starting dialysis with a central venous catheter (CVC) or a non-permanent access, having a low Alb (<3.5 g/dl) and/or low Phos (<3.5 mg/dl), or having “inadequate pre-dialysis care”.[18,27,28] Early HD mortality is associated with hospitalizations for CV events, infections, and vascular access complications.[19]

Cardiovascular instability is a known risk factor for mortality in prevalent HD patients. The prevalent dialysis period includes patients who have been on dialysis for greater than 120 days. In 1998 Zager, et. al. described a “U” curve for the relationship between

dialysis systolic blood pressure (SBP) and CV mortality for prevalent patients.[29] Subsequent studies have shown a "reverse epidemiology" in prevalent HD patients with increased mortality risk for patients with low and normal BP.[30] BP variability between HD treatments (inter-dialytic) and during HD treatment (intra-dialytic) is also associated with adverse patient survival.[31,32] Most studies examine prevalent patients, not patients in the early weeks of dialysis and they describe long-term mortality risk at 1 and 2 years after dialysis start. No previous study has described SBP during the first weeks of dialysis and the impact on short-term survival in this critical, high mortality period. This is the topic of **Chapter 2** which describes SBP in the weeks after dialysis start and short-term mortality risk in the following week.

5. Dialysis transition

Studies have examined laboratory parameters reflecting nutrition, inflammation, BMM, and CV status and the association with subsequent patient outcomes in incident and prevalent dialysis patients. Few studies examine these factors through late stage CKD to the transition to dialysis start, yet it seems likely that there are modifiable factors in late stage CKD that impact transition and incident dialysis outcomes.
In the U.S. the Veterans Administration CKD database combined with ESRD data from USRDS creates a dataset that transitions from CKD to dialysis. O'Hare, et. al. used this dataset to describe clinical and care delivery characteristics for this patient population through the transition to dialysis start.[33] Such studies highlight CKD parameter trajectories that impact dialysis start and early dialysis outcomes. In **Chapter 3** we use a unique CKD dataset to add to the scarce literature on pre-dialysis trajectories of key clinical parameters and mortality in the early months after dialysis start. Such research may help predict or anticipate early dialysis outcomes or even provide a "window of opportunity" to change CKD trajectories and improve incident dialysis outcomes.

6. The impact of pre-dialysis care

Despite routine reporting of eGFR when a serum creatinine is completed, many people in the U.S. are undiagnosed or unaware of their CKD. This lack of awareness contributes to nearly 36% of patients starting dialysis with no or an unknown amount of nephrology care and about 13% of patients starting with less than 6 months of nephrology care.[6]
Early CKD nephrology management focuses on slowing CKD progression and late stage CKD care aims to smooth the transition to dialysis treatment start to reduce incident dialysis mortality. Even when patients are aware of CKD and are under nephrology care, it is difficult to provide care that leads to an optimal dialysis start for treatment of ESRD.[6] Many patients who are referred early to nephrologists and receive over a year of nephrology care before dialysis start, still have a suboptimal transition.[36] Late stage

CKD patients expecting to start dialysis in the next 6-12 months need support in making treatment option decisions and preparing for an optimal dialysis start.[34,35]
An optimal dialysis start includes starting with a permanent access in an outpatient setting with a home modality if possible. A suboptimal dialysis start results in low utilization of home therapies at dialysis start and increased early dialysis period mortality.[6] Multi-disciplinary nephrology practice care is associated with an optimal dialysis start and improved dialysis outcomes.[34] Patients receiving significant nephrology care are more likely to have dietary counseling, treatment for anemia with an erythrocyte stimulating agent (ESA), and are more likely to start HD with an arteriovenous fistula (AVF).[6]
In general, pre-dialysis nephrology care is associated with improved early dialysis outcomes, but the frequency and quality of this nephrology care is important. In a Canadian study 50% of patients received nephrology care for more than 12 months, but only 43% of those patients had an optimal start.[34] Factors improving the likelihood of an optimal start include support for helping patients make timely modality decisions, coordination of permanent access surgery, and predicting and monitoring CKD progression.[34]
Studies of cumulative (>10 nephrology visits in the 3 years before dialysis start) and critical period care (being seen more than 3 times in the 6 months before dialysis start) show a correlation with dialysis outcomes. A high number of cumulative and critical period visits are associated with lower first dialysis year mortality, a lower incidence of hospitalization at dialysis start, and a greater likelihood of starting dialysis with a permanent access.[36]
There is a need to determine the best late stage CKD care delivery models and interventions to improve the likelihood late stage CKD patients will have an optimal transition to dialysis start. **Chapter 4** describes a successful data-driven, late stage CKD case management care model that reduces dialysis transition risk factors and improves incident dialysis outcomes.

7. First modality and outcomes

HD and PD differ in technical aspects of dialysis and ultrafiltration, site of care delivery, and in social aspects of self-care. In general, the starting dialysis modality in the U.S. is considered a patient choice although it is influenced by pre-dialysis care including CKD awareness, access to healthcare, and patient education. Studies assessing dialysis patient outcomes based on a starting modality of HD versus PD show mixed results. Some studies show an early survival advantage for patients starting PD.[37-39] Other studies conclude that there is no survival advantage for either modality.[40]
CKD patient characteristics that may influence modality selection remain poorly understood. Although fluid overload is associated with increased ESRD mortality, little is known about the volume status of CKD patients in the months before they start

dialysis on HD or PD and little is known about the changes in volume status in the early dialysis weeks comparing the two modalities. Inflammation is associated with adverse dialysis outcomes and there is concern that initiation of PD is associated with chronic inflammation related to presence of the PD catheter and instillation of non-biocompatible PD fluids.[41] The inflammatory status of patients in the months before starting and during the transition to PD or HD is poorly understood.
Some studies suggest that patients with more rapid CKD progression are more likely to start HD and have higher early dialysis mortality associated with clinical factors that contributed to CKD progression.[42] Research on CKD clinical trajectories and the associated transition to dialysis is scarce. Specifically, there is an absence of data for HD versus PD starters through the dialysis start transition. **Chapter 5** uses a unique CKD dataset to examine CKD parameters and trajectories associated with starting HD versus PD. In this study continuous data from CKD through the first 12 months of dialysis shows outcomes in key clinical domains in the first dialysis year for PD versus HD starters.

8. First modality and Health Related Quality of Life

The World Health Organization (WHO) defines QOL as, "….an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".[43,44] Measuring Health Related QOL (HRQOL) in chronic illness takes into account the patient's perceptions of health, life satisfaction, and sense of well-being as well as physical function.[44] These patient-reported measures of HRQOL are associated with clinical outcomes including hospitalization and mortality.[45-47]
Generic HRQOL surveys such as the Medical Outcomes Study Short Form-36 (SF-36)have been developed and validated in the general population with chronic illness.[44] Disease specific HRQOL surveys are available including the Kidney Disease QOL (KDQOL) survey which has been validated in ESRD.[44,48] This instrument includes some generic measures from the SF-36 plus items relevant to ESRD.[44] In keeping with the desire to measure patient perceptions of health and treatment, KDQOL has 36 questions that divide into 5 main subscales:[49]

- Physical Component Summary (PCS) score
- Mental Component Summary (MCS) score
- Burden of kidney disease
- Symptoms and problems
- Effects of kidney disease on daily life

In ESRD the level of satisfaction with treatment modality, the perceived burden of the treatment, treatment side effects, the quality of caregiver and provider relationships, and symptom control all are factors that contribute to HRQOL.[44] It is unclear what

proportion of differences in PD versus HD outcomes is technique related or predetermined by CKD patient factors associated with a starting dialysis modality. In addition, patient quality of life may be very different starting a home therapy versus an incenter HD therapy and the impact on outcomes based on patient QOL is not known.
Previous studies compare HRQOL in incenter HD versus home PD treatment, but many of these studies are cross-sectional only, were completed many years ago, or included a small cohort of patients.[46,50-53] Results are mixed with some studies suggesting improved HRQOL scores for patients on PD[50,52,53] and others suggesting that HD patients have better PCS scores.[46] In **Chapter 6** we provide an HRQOL assessment using a large national patient database. In this study we examine HRQOL by first dialysis modality at the time of dialysis start and provide longitudinal follow-up to examine HRQOL change for HRQOL change for incenter HD versus home-based treatments.

9. Summary

Over 100,000 new patients start dialysis therapy every year in the U.S. The transition to dialysis treatment is a critical period associated with the highest mortality. This transition period is difficult to study due to lack of continuous data from late stage CKD through dialysis start. Studies of clinical parameters from early dialysis suggest that patient characteristics at the start of dialysis treatment impact dialysis outcomes in the incident period and throughout the first year of dialysis. It is also likely that late stage CKD trajectories and CKD nephrology care influence and are predictive of early dialysis outcomes and first dialysis modality choices. Starting with HD versus PD may impact survival either because of dialysis technique differences or because of differences in patient and clinical care CKD characteristics. Early HD versus PD outcomes may also be impacted by QOL factors as patients transition to dialysis start.

10. Aim of this thesis

The aim of this thesis is to examine patient and treatment characteristics from CKD through the time of dialysis start transition. Risk domains are studied continuously through late stage CKD and the incident dialysis period. CKD interventions that mitigate risk at the start of dialysis are examined for practices that improve the likelihood of an optimal dialysis start. The thesis examines a rarely studied trajectory of transitioning from CKD to an HD or PD therapy and how incenter or home-based treatments impact patient quality outcomes including QOL.

11. Outline of this thesis

In **Chapter 2** a large U.S. dialysis dataset is used to expand knowledge about a prevalent, long-term mortality risk parameter by using data at the time of transition to dialysis start to examine the relationship between low pre-SBP and short-term mortality for patients in the first weeks of HD. **Chapter 3** adds to very scarce literature about clinical parameter trajectories including SBP, Alb, Phos and Wt through late stage CKD and the transition to the early dialysis period and the association with patient survival.

Recent studies suggest that late stage CKD care and clinical parameters at the start of dialysis impact early dialysis outcomes. **Chapter 4** adds to the literature describing an effective case management program to improve pre-dialysis care and outcomes at the time of transition to dialysis start.

Chapter 5 uniquely studies key clinical parameters in CKD for patients who start HD versus PD and how those parameters change in the early dialysis period. This study is accompanied by data in **Chapter 6** that examines QOL changes for patients starting home-based versus incenter treatments

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Chapter 2

The association of weekly pre-hemodialysis systolic blood pressure and following week mortality

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Abstract

Background
Few studies examine the impact of systolic blood pressure (SBP) on mortality in the incident hemodialysis (HD) period, and throughout the first HD year. This large retrospective observational study analyzes the impact of "current" and cumulative low preSBP <110 mmHg (L), and variations in preSBP on short-term (1 week) mortality over the first HD year.

Methods
In 269397 patients, weekly mean preSBP for HD weeks 1 to 51 was categorized into L or high preSBP ≥110 mmHg (H) for each patient. A generalized linear model (GLM) was used to compute the probability of death in the following week. The model includes age, gender, race and three preSBP-related parameters: (a) percent of prior weeks with L preSBP; (b) percent of prior weeks with switching between L to H; (c) "current" week's preSBP as a binary variable. Separate models were constructed that include demographics and BP-related parameters (a), (b), and (c) separately.

Results
In a model combining (a), (b), and (c) above, "current" week L preSBP is associated with increased odds ratio for following week mortality throughout the first HD year. The percent of prior week's L and more switching between L and H are less significantly associated with short-term mortality. In models including (a), (b), and (c) separately, "current" L preSBP is associated with higher mortality.

Conclusion
This study confirms an association of L preSBP with increased short-term mortality which is maintained over the first HD year. Percent of L preSBP in prior weeks, switching between L and H, and "current" week L are all associated with short-term mortality risk, but "current" week L preSBP is most significant.

Introduction

In the general population and in chronic kidney disease (CKD), treatment of high blood pressure is important to prevent cardiovascular and cerebrovascular morbidity and mortality, but this may not be true for hemodialysis (HD) patients. While blood pressure (BP) guidelines in prevalent HD patients focus on BP control to avoid hypertension, recent studies suggest a "reverse epidemiology" for BP in HD patients. Systolic BP (SBP) levels which are considered "normal" in the general population are associated with adverse outcomes for incident HD patients and throughout the first year of HD.[1] A landmark study by Zager described a "U-shaped" curve relationship between HD BP and mortality with pre-dialysis SBP (preSBP) <110 mmHg associated with increased mortality.[2] Subsequent studies also describe the association of SBP <110 mmHg and increased mortality.[3] In a 2006 study, incident HD patients meeting the recommended SBP target of <140 mmHg had worse one year survival than patients with "elevated" SBP >140 mmHg.[1]

In addition to the mortality association with absolute preSBP levels in the incident HD period, BP trends over time are important. It has been observed that recent SBP was more sensitive than remote SBP for one year survival and decreasing SBP is associated with poorer long-term survival.[1] In a study evaluating incident HD patients, greater mortality in the first year of HD was found for patients with temporal BP changes, either SBP decrease or increase compared to stable SBP, even when compared to low absolute BP.[4]

PreSBP variability is also reported to increase all-cause mortality in prevalent HD patients. In an analysis using data from the HEMO study, visit to visit preSBP variability was associated with cardiovascular mortality risk and the impact was enhanced by lower baseline preSBP.[5] Flythe et al. evaluated intradialytic SBP variability in prevalent HD patients during a 30 day study period and showed an association of increased SBP variability with both all-cause and CV mortality risk.[6]

This large retrospective observational study examines the relationship between preSBP <110 mmHg (L preSBP) and short-term mortality outcomes. We aim to fill an information gap by including patients from the first date of dialysis (FDD) throughout the first year of HD including the critical incident HD period. We analyze the impact of the percent of L preSBP cumulative over time, the switching between L and preSBP ≥110 mmHg (H preSBP), and the "current" week L preSBP on the mortality risk in the following week. Study of this ultra-short-term mortality risk may provide insights for clinicians rounding in the dialysis facility. L preSBP as well as preSBP variations which can easily be recognized during clinical rounds could be of importance for the clinician in identifying patients at immediate mortality risk.

Methods

In this study we analyzed data from 269,397 FMCNA incident HD patients who initiated dialysis between Jan 1, 2004 and Nov 30, 2014, survived more than 7 days on HD, and had at least one preSBP measurement. PreSBP was measured at the start of each HD treatment and recorded in an electronic treatment record. For each week, we computed mean preSBP as the average of all treatments during the week (irrespective of the number of treatments); week 1 is the first week of chronic outpatient HD. For each of the first 51 weeks on HD, we categorized patients into two groups of mean preSBP: patients fell into the "Low" (L) group with average preSBP <110 mmHg or the "High" (H) group with preSBP ≥110 mmHg. During the first 51 weeks, patients are likely to have a variety of patterns of H and L preSBP values. For example, some patients may always remain in the H group, while others may always remain in the L group; many patients would experience changes in H and L preSBP values over time. To illustrate this, the following section provides a specific example of how these are computed.

Based on this, we computed three separate preSBP related variables for each patient for each of the first 51 weeks:

a. Percentage of weeks with preSBP<110 mmHg up to each week analyzed
b. Percentage of weeks when patients' preSBP changed from H to L or vice versa
c. Binary variable which indicates whether the "current" week's preSBP is below 110 mmHg

For each week, we used a generalized linear model (GLM) to compute the probability of death in the following week. Four different models were constructed. The first three include age, gender, and race as well as (a), (b), and (c) separately. Since (a), (b), and (c) are related, an additional model that includes age, gender, race and (a), (b), and (c) was constructed. This means that 204 distinct GLM models were completed: three models 51 times for each of the preSBP variables and one model 51 times that combines all three preSBP variables. After IRB review this research was determined to be exempt from IRB approval.

Example of PreSBP Calculation

As an example, for a patient who has survived 8 weeks we would like to determine their risk of death in week 9. The patient's preSBP pattern is as follows:

- Week 1: L (preSBP<110 mmHg)
- Week 2: H (preSBP≥110 mmHg)
- Week 3: L
- Week 4: L
- Week 5: H

- Week 6: H
- Week 7: L
- Week 8: L

This pattern can be expressed as follows: LHLLHHLL. In the above example, the patient was dialyzed for eight weeks with 5 weeks preSBP being L and the most recent (week 8) preSBP also being L. The patient's preSBP switched from H to L or vice versa 4 times (week 1 to week 2; week 2 to week 3; week 4 to week 5; week 6 to week 7). Three preSBP variables in the model are calculated as follows:

1) percent of prior 8 weeks with L preSBP (<110 mmHg): the number of low weekly preSBP measurements divided by 8, i.e.,

$$\textbf{Percent of prior 8 weeks with Low preSBP} = \frac{\textbf{number of L preSBP}}{8} = \frac{5}{8} = 62.5\%$$

2) percent of prior weeks when patients' preSBP switched from L to H or vice versa: the number of switches divided by 7 (the maximum of possible switches), i.e.,

$$\textbf{Percent of prior 8 weeks with switches} = \frac{\textbf{number of switches}}{7} = \frac{4}{7} = 57\%$$

3) binary variable if the week 8's preSBP was L: equal to 1 if week 8's preSBP is below 110 mmHg, 0 if week 8's preSBP is equal or above 110 mmHg.

$$\textbf{Indicator of the week 8 preSBP was L} = \begin{cases} 1, & preSBP < 110\,mmHg \\ 0, & preSBP \geq 110\,mmHg \end{cases} = 1$$

Results

Baseline patient data are shown in Table 2.1.

Overall mortality rates peak at week 2, rapidly decline in the first 2 months and continue to decrease as the weeks from first outpatient dialysis treatment increase (Figure 2.1).

In a model repeated weekly with the historic percent of previous L preSBP, the historic percent of switches between L and H, and most recent or "current" week preSBP <110 mmHg, all co-variates are independently associated with increased mortality in the following week (Figures 2.2, 2.3, 2.4). Risk of death is 20 to 50% higher in the following week for every additional 10% more previous weeks with preSBP <110 mmHg (Figure 2.2). The risk of death is 10 to 90% higher in the following week for every 10% more previous weeks where preSBP changes from H to L or vice versa (Figure 2.3).

Table 2.1 Description of the study cohort.

Number of pts	269,397
Age	63.26 (15.06)
White %	68%
Black (%)	29%
Hispanic (%)	14%
Male (%)	57%
Catheter access (%) *	66%
Pre-dialysis SBP (mmHg) *	143.63 (21.62)
Pre-dialysis DBP (mmHg) *	74.75 (13.14)
BMI (kg/m^2) *	29.13 (1481.58)
Treatment time (mins) *	217.96 (29.66)
Interdialytic weight gain (kg) *	1.87 (1.06)
Ultrafiltration rate (mL/hr/kg) *	6.1 (12)
Albumin (g/dL) *	3.44 (0.52)
Hgb (g/dL) *	10.18 (1.26)
Arrhythmias (%)	5%
Cerebrovascular disease (%)	3%
CHF (%)	11%
Hypertension (%)	23%
Ischemic heart disease (%)	9%
Diabetic (%)	63%
Average number of comorbidities	6.41 (9.21)

* Value or average in the first 30 days of chronic outpatient dialysis with standard deviation in parentheses for continuous variables.

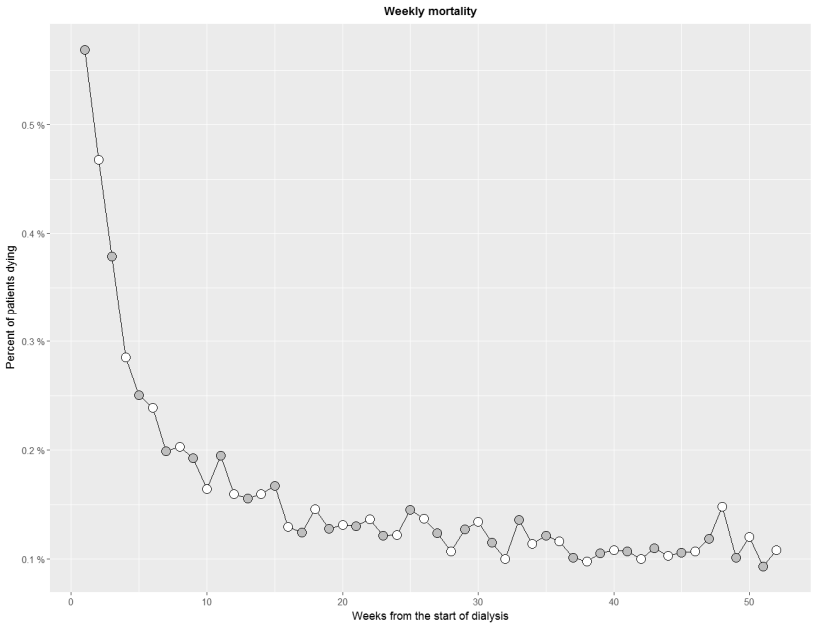

Figure 2.1 Proportion of patients dying over 52 weeks (from all causes).

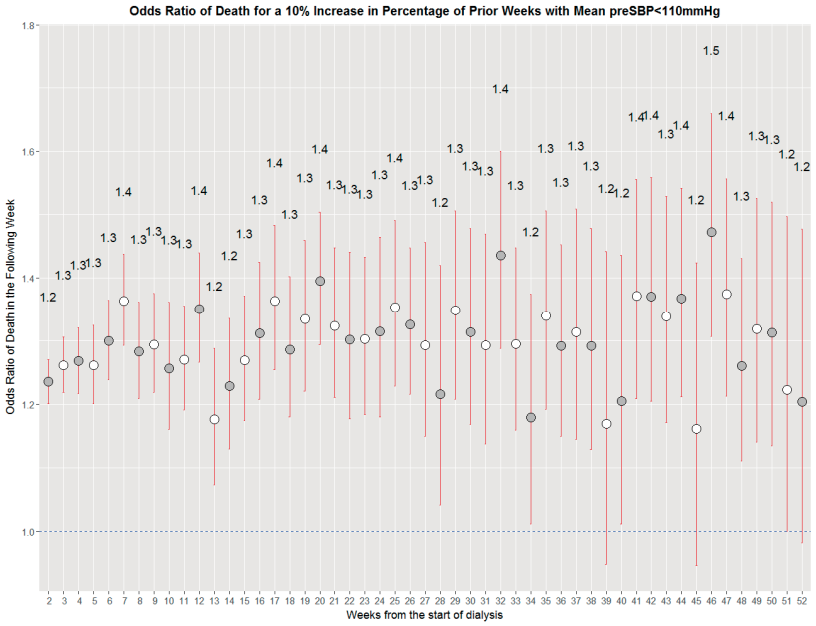

Figure 2.2 Effect of historic percent of L preSBP in all prior weeks on following week mortality.

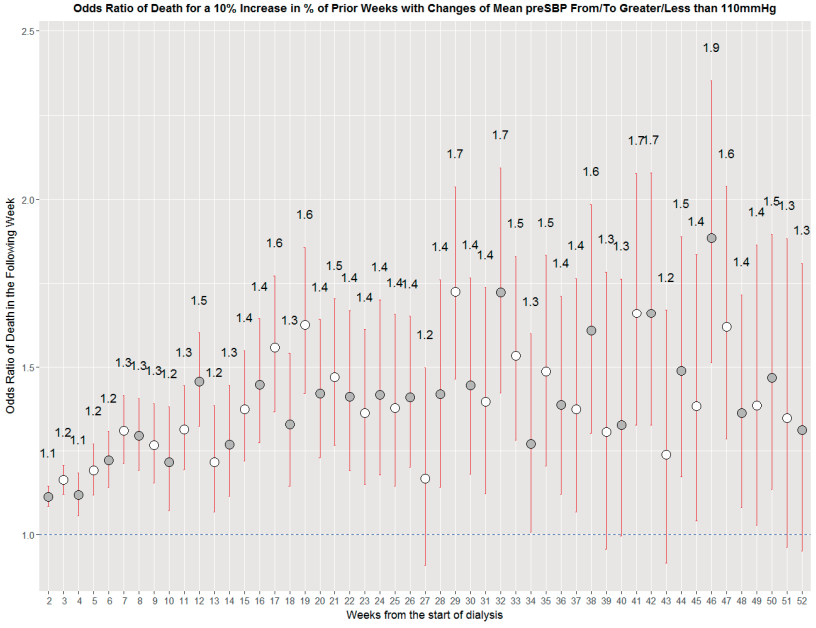

Figure 2.3 Effect of historic percent of switching between L and H preSBP in all prior weeks on following week mortality.

While a patient's L or H preSBP history impacts ultra-short-term mortality the risk of death in the following week for patients whose most recent preSBP <110 mmHg with odds ratio between 2.6 and 12.4 is most impactful throughout the first year of HD (Figure 2.4).

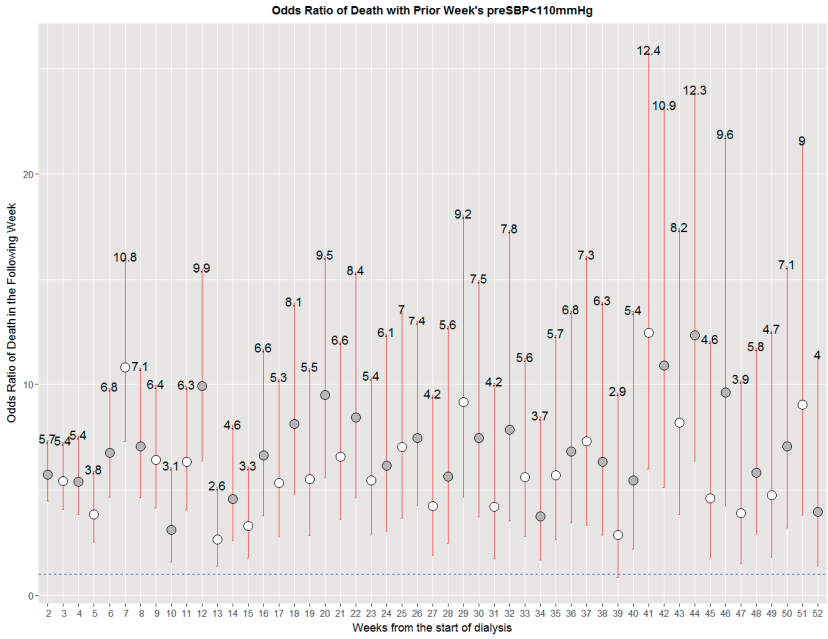

Figure 2.4 Effect of "current" week L preSBP on following week mortality.

To determine the independent impact of each of the three preSBP variables, a three-covariate model was created. Figures 2.5, 2.6, and 2.7, demonstrate the impact of each of the three preSBP variables when controlling for the other two. While the historic percent of previous L preSBP (Figure 2.5) and the historic percent of switches between L and H (Figure 2.6) appear to generally have a negative impact on survival, most weeks are not statistically significant. "Current" week preSBP <110 mmHg appears to still have a negative impact on short-term mortality throughout the 52-week period (Figure 2.7).

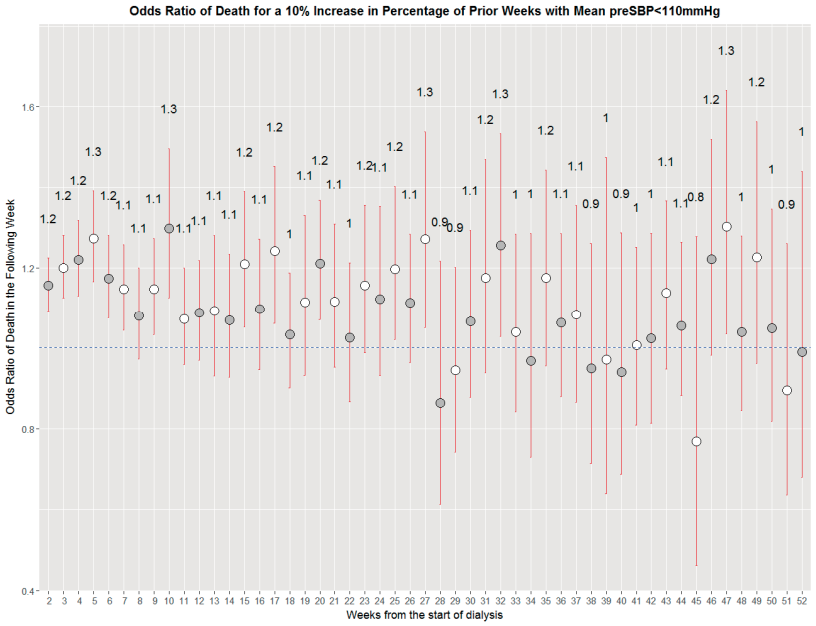

Figure 2.5 Independent effect of historic percent of L preSBP in all prior weeks on following week mortality (controlled for percent of weeks with preSBP switching and current L preSBP).

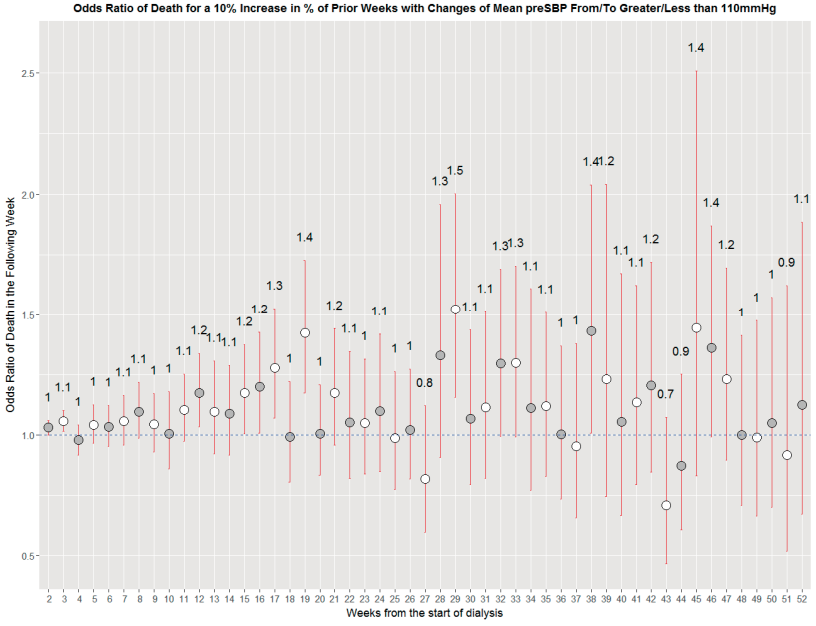

Figure 2.6 Independent effect of historic percent of preSBP switching in all prior weeks on following week mortality (controlled for percent of weeks with L preSBP and current L preSBP).

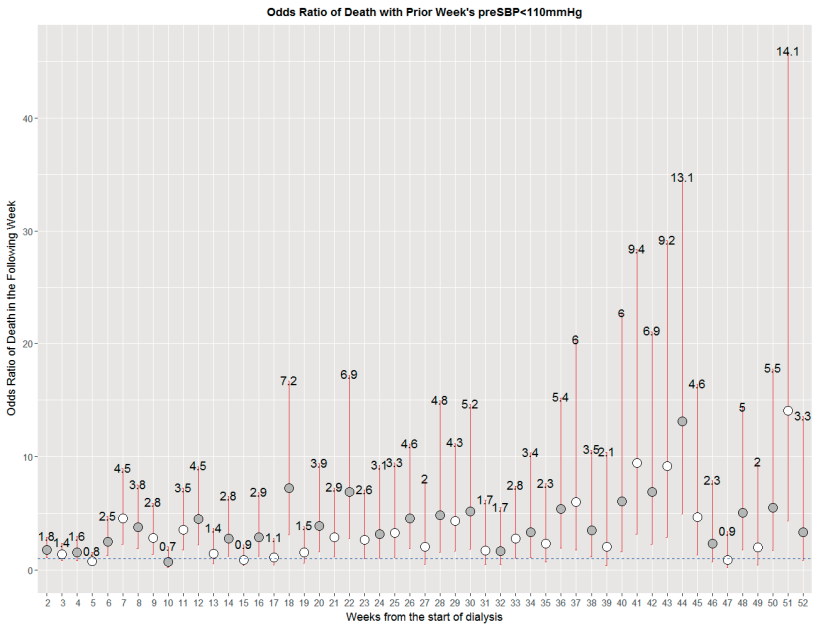

Figure 2.7 Independent effect of current week's L preSBP on following week mortality (controlled for percent of weeks with L preSBP and percent of weeks with preSBP switching).

Discussion

This large retrospective observational study of HD patients during the first year of treatment examines the association of L preSBP, defined as preSBP <110 mmHg, and ultra-short-term mortality risk (mortality risk in the following week). In this study weekly independent models were used to determine the impact of "current" L preSBP on following week mortality. Models including the historic percent of L preSBP and percent of switching from L to H facilitate including the historic pattern of preSBP for patients representing BP trends and variability over time.

We confirmed high relative mortality in the early vintage period in HD which was also observed in other studies.[7,8] In addition this analysis suggests that "current" week L preSBP is associated with ultra-short-term mortality risk throughout the first year of HD, even though the greatest absolute mortality risk is in the early HD weeks. The non-time overlapping 3 covariate model suggests that historical L preSBP and preSBP variation impact short-term mortality risk, but "current" L preSBP impacts short-term mortality the most. This suggests that a patient who has had historically H preSBP, but

then has an average L preSBP in a given week is at risk for increased mortality in the following week.

This study adds to the literature by using a large dataset for weekly mortality risk prediction. PreSBP patterns were assessed weekly from the start of HD, including the first 90-day period, which is often omitted from studies. We focused not only on "current" preSBP levels, but also on historic preSBP and variations in preSBP, as it has been observed that BP trends and variability over time and not simply absolute BP is related to adverse outcomes.[4] Historic preSBP patterns and variations in preSBP after 4 weeks become too complicated for visual display, so we focused on GLM analysis to identify whether historic L preSBP, historic variations in preSBP, or "current" week preSBP was most consistently related to ultra-short-term mortality.

Management of BP in the general population, CKD, and HD patients remains largely focused on interventions and treatment for elevated BP. While this is appropriate in mitigating pre-dialysis intermediate or long-term risk, large epidemiological studies have suggested that low and even low-normal BP (<110-120 mmHg) convey an even higher mortality risk for HD patients.[1-3,9,10] Li et.al. provided an analysis showing a "robust" association of normal and prehypertension BP with mortality risk in dialysis patients.[1] These authors suggest, contrary to guidelines for the general population, practicing clinicians should consider patient-specific evaluations for dialysis patients with "low" or "low-normal" preSBP.[1]

Studies assessing BP trends during the first year on HD have yielded conflicting results. Sipahioglu, et.al. describe an association of both low (baseline preSBP <120 mmHg) and declining preSBP with increased mortality at 6 and 12 months.[10] Raimann et al. also showed the highest mortality in the quartile of patients who experienced the largest decline in BP during the first year on HD.[4] This contrasts with studies from the Tassin group, in which patients in the tertile experiencing the largest decline in preSBP pressure during the first year on HD had the best outcomes.[11]

Increased variability in preSBP, expressed as the standard deviation or residuals of the mean in a linear regression, and intradialytic SBP are risk factors for adverse patient outcomes.[6,12,13] The reasons for this have not been completely elucidated, but associations with dialysis treatment ultrafiltration, heart failure, diabetes, and central venous catheter use have been described.[5,14] Other clinical factors associated with BP variability in HD include a reduction in buffering capacity of the arterial wall by increased vascular stiffness in combination with osmotic or fluid changes.[6,15] We did not study variability or slopes per se, but the results of the present study are in basic agreement with these previous studies. However, we assess the ultra- short-term risk associated with weekly changes in preSBP and to the best of our knowledge this is the first study describing this mortality risk.

Low BP in HD may impair cerebral or cardiac perfusion increasing mortality risk.[16] Underlying comorbidity, such as heart failure, can cause low BP and the subsequent increased mortality risk. In observational studies like ours it cannot be determined if

L preSBP causes the increased mortality risk or if it is a marker for underlying co-morbidity that is associated with increased mortality risk. In particular in this study we do not have data to confirm patient volume status at the time of L preSBP, so the impact of volume overload coupled with L preSBP cannot be assessed independently.[17] Therefore, we agree that low preSBP values or declining preSBP trends should always be interpreted in the clinical context of the patient and should trigger a detailed clinical assessment.
Strengths of this study include the large sample size and the inclusion of patients geographically distributed across the U.S. Data was collected from the first date of outpatient HD, so this analysis includes patients throughout the incident dialysis period.
Limitations of the study include the absence of information on volume status which would help identify patients for whom a low or high BP is a reflection of volume status. We also arbitrarily selected the preSBP level of 110 mmHg as low or "L", however, this is based on the study of Zager et al..[2] We also lack data on medication usage and cardiac structure or function.

Low preSBP values were observed in a relatively small percentage of patients, although due to the size of the database, the number of patients was still relatively large in an absolute sense. We did not correct for different comorbidities or vascular access in this study, as these might be in the causal pathway of the relation between low preSBP and outcome and as such are not confounders. The lack of adjustment does not preclude the usefulness of low SBP values as markers for outcome.
Despite these limitations this study shows an observational association with a commonly available clinical parameter which can alert clinicians to the need for additional evaluation. This paper may also serve as a proof of concept for the persistent short-term risk associated with low preSBP.

In conclusion, this large retrospective observational study reports an association of historic L preSBP, preSBP variability between L and H, and "current" L preSBP with ultra-short-term mortality risk. The "current" L preSBP seems most consistently associated with mortality in the following week throughout the first year of HD. This analysis offers an association of a routinely observed clinical parameter with short-term mortality risk raising awareness of the need for clinical assessment of HD patients with L preSBP.

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Chapter 3

Clinical parameters before and after the transition to dialysis

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Abstract

Background

The transition from pre-dialysis chronic kidney disease (CKD) to post-dialysis start is a critical period associated with high patient mortality and increased hospital admissions. Little is known about the trends of key clinical and laboratory parameters through this time of transition to start dialysis.

Methods

From 12, 185 patients, de-identified data including demographics, vital signs, lab results, and eGFR from the Fresenius Medical Care-CKD Registry were analyzed to determine trends in clinical and laboratory parameters through the time of transition from 12 months pre-dialysis start to 12 months post-dialysis start. Trends in key clinical and laboratory parameters associated with cardiovascular, nutritional, mineral metabolism and inflammatory domains were examined in association with the transition to dialysis start and first year dialysis survival.

Results

All parameters show divergence for patients who survive versus do not survive the first year of dialysis. Of note, during pre-dialysis CKD the absolute systolic blood pressure (SBP) level is lower and the slope for SBP decline is significantly steeper for patients who do not survive the first year on dialysis.

Conclusion

This study uniquely demonstrates the trajectories of key parameters though the transition from pre- to post-dialysis start. Significant differences are noted in the pre-dialysis period for patients who survive versus those who do not survive the first year of dialysis. Early recognition of adverse trends in the pre-dialysis period may create opportunity to intervene to improve early dialysis outcomes.

Introduction

Transition from late stage Chronic Kidney Disease (CKD) to dialysis start is a critical period for end stage renal disease (ESRD) patients.[1,2] Maintaining data continuity through the transition from pre- to post-dialysis start is complex since clinical data which spans pre-dialysis nephrology practice care to post-dialysis start is usually not contained in a single database.[3] Therefore, little is known about the continuity of trajectories of key clinical and laboratory parameters before and after the start of dialysis. A better understanding of the trajectories of these parameters is important for obtaining pathophysiological insight into this critical transition period. It is also important for detecting early signs associated with adverse outcomes.

The 2014 and 2015 United States Renal Data System (USRDS) Annual Data Reports (ADRs) included data from the Transition of Care in Chronic Kidney Disease (TC_CKD) Special Study Center.[4,5] To examine the impact of late stage CKD care on dialysis transition, the study group linked USRDS ESRD data with U.S. Veterans Affairs and regional Southern California Kaiser Permanente (KP-SC) non-dialysis dependent CKD data. Analysis of these data highlights use of medications and hospitalization patterns in the pre- (prelude) and post- (vintage) dialysis period including clinical and laboratory parameters up to the transition to dialysis start.[5] Large provider networks such as Veterans Administration or networks using the same or integrated Electronic Health Records (EHR) systems are well suited for studying the transition from late stage CKD to ESRD.

While this USRDS transition data is notable, most U.S. CKD patients receive care in nephrology practices that are not part of an integrated healthcare system. Also, the USRDS transition study does not include data on the trend of clinical parameters in the post-dialysis start period or provide a comparison between patients who do or do not survive the early vintage period.

Our study includes a geographically diverse U.S. patient population receiving care from typical nephrology practices. We aim to describe clinical and laboratory parameters in the 12 months before (-12 months) and the 12 months after (+12 months) starting dialysis in a large U.S. CKD population who have received at least 12 months of pre-dialysis nephrology care. The trajectory of pre-dialysis clinical parameters is compared for patients who survive and do not survive the first 12 months following the start of dialysis.

Methods

The Fresenius Medical Care-CKD Registry includes data for over 500,000 patients geographically dispersed in the U.S. with CKD or ESRD who receive care from

nephrology practices utilizing a nephrology-focused EHR. The Registry conforms to Safe Harbor de-identification standards; no identifying data is harvested and all event dates are represented by a year and the number of days since the patient had an initial encounter in the nephrology office. To comply with the U.S. Health Insurance Portability and Accountability Act data on patient's age in this de-identified dataset was capped at 90 years, which did not affect the stratification. Data elements including demographics, vital signs, lab results, and eGFR (calculated using the CKD-EPI and/or MDRD4 equation) are placed in the registry. After IRB review this research was determined to not require IRB approval.

All clinical data reported here originates in a nephrology-focused EHR used by providers in 39 U.S states and Puerto Rico. Post-dialysis start laboratory data is collected during dialysis treatments as part of routine ESRD laboratory testing and is imported into the nephrology practice EHR. De-identified patient data from the EHR is swept into the Fresenius Medical Care-CKD Registry on a weekly basis creating a large CKD database. Hence, the Fresenius Medical Care-CKD Registry represents a clinical data repository that remains intact through the transition from late stage CKD to ESRD.

For this analysis, we include data on all CKD patients who were seen as a CKD stage 1 to 5 patient in the twelve months before the start of dialysis and at least once as an outpatient chronic ESRD patient between 2010 and 2015. We assessed the first date of chronic dialysis treatment as a date when a patient first received outpatient hemodialysis (HD) or peritoneal (PD) treatment or first inpatient dialysis treatment that was immediately followed by outpatient dialysis therapy. Patients' survival status after initiating dialysis was assessed based on whether a patient died in the first calendar year following dialysis initiation. All clinical data is collected from the nephrology practice EHR.

Key parameters involving cardiovascular, nutritional, inflammatory and mineral metabolism status evaluated in this study are of importance because of their known association with dialysis patient outcomes. For all patients we observed laboratory and clinical parameters during the 12 months before and 12 months following dialysis initiation. Patients' blood pressure and body weight were assessed only in the nephrology office both before and after dialysis initiation. Patients who died in the first 12 months after starting dialysis are stratified as "non-survivors". "Survivors" include patients who are still active on dialysis at 12 months after the start of dialysis. For each patient, we average laboratory and clinical data in monthly intervals before and after dialysis initiation.

Slope of changes in patient parameters are computed for each laboratory and clinical parameter in the 12 months before dialysis initiation using simple linear regression per patient. Resulting monthly changes in patient parameters prior to dialysis initiation are compared using unpaired t-tests. Comparisons of other continuous variables are conducted using unpaired t-tests. SAS version 9.3 (Cary, NC) software was used for statistical analysis.

Results

We studied 12,185 patients with a mean age of 65.2 years of whom 56% were male and 29% black. Of those studied 1,453 died in the first 12 months on dialysis (12%). The majority of patients started dialysis with HD modality (90%). Further patient characteristics are displayed in Table 3.1.

Table 3.1 Demographic characteristics.

	All	Survived	Died	Difference (95% CI)	p-value*
Number of patients	12185	10732	1453		
Number of HD patients	10989	9606	1383		<.0001
Age	65.2 (13.3)	64.8 (13.4)	68.1 (12.1)	-3.24 (-3.99 to -2.5)	<.0001
Black (%)	29%	29%	29%	0.4 (-2 to 2.9)	0.7247
Male (%)	56%	56%	55%	0.5 (-2.3 to 3.2)	0.7412
Systolic blood pressure (mmHg)	141.4 (20.9)	141.8 (20.7)	138.3 (21.8)	3.52 (2.27 to 4.78)	<.0001
Body weight (kg)	89.5 (25.2)	89.8 (25.2)	87.2 (24.7)	2.55 (1 to 4.1)	0.0011
Albumin (g/dl)	3.54 (0.52)	3.55 (0.51)	3.48 (0.54)	0.07 (0.02 to 0.12)	0.0065
Sodium (mmol/l)	139.1 (3.5)	139.2 (3.5)	138.9 (3.5)	0.26 (0.02 to 0.5)	0.0337
White Blood Cell count ($x10^9$/l)	7.7 (4.7)	7.6 (2.9)	8.1 (11.1)	-0.44 (-0.76 to -0.12)	0.0068
Phosphorus (mg/dl)	5.09 (1.31)	5.11 (1.31)	5 (1.32)	0.11 (0.02 to 0.2)	0.017

Averages over the 3 months before starting dialysis; mean (±standard deviation). *P-value compares patients who survived vs those who died.

Systolic blood pressure

Mean systolic blood pressure (SBP) is elevated at 12 months before dialysis start (-12 months) and remains stable as dialysis approaches with a mean decline per month of 0.05 mmHg/month (Table 3.2). Dialysis initiation is associated with a significant drop in SBP (Figure 3.1). SBP trends differ for survivors versus non-survivors throughout the 12 months before dialysis start: patients who died within 12 months after dialysis initiation have a decline in their BP before dialysis start of 0.44 mmHg/month while those who survived have a stable BP prior to dialysis start. The difference in slopes between the two groups is significant prior to dialysis start. (Table 3.2, Figure 3.1).

Table 3.2 Average monthly changes in patient parameters in 12 months prior to dialysis initiation.

	All	Survived 12 months on dialysis	Died within 12 months on dialysis	p-value*
eGFR (ml/min/month)	-0.67	-0.66	-0.72	0.1265
Systolic BP (mmHg/month)	-0.05	-0.01	-0.44	0.0001
Weight (kg/month)	-0.12	-0.09	-0.08	0.8425
Albumin (g/dl/month)	-0.01	-0.011	-0.011	0.9802
WBC (10^9/l/month)	0.02	0.02	0.07	0.3454
Serum sodium (mmol/l/month)	-0.05	-0.04	-0.09	0.0698
Phosphate (mg/dl/month)	0.07	0.07	0.07	0.7696

Monthly average changes are computed using simple linear regression in 12 months prior to dialysis initiation on a per-patient basis. *P-value compares slopes in patients who survived vs those who died.

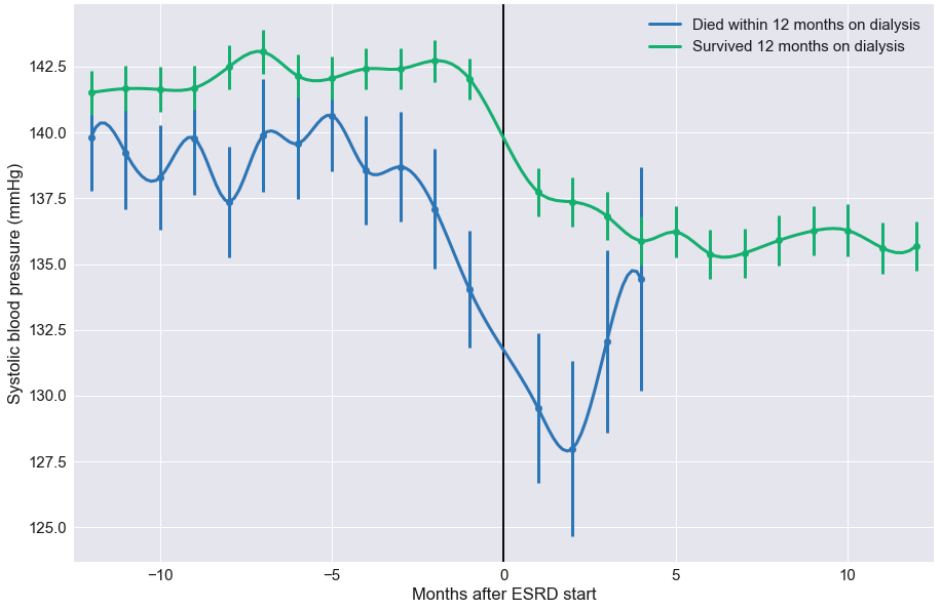

Figure 3.1 SBP in the 12 months before and after HD start for survivors and non-survivors.

Weight

Mean body weight (Wt) is stable at -12 months before dialysis start, but decreases at the initiation of dialysis by about 6 kg. Mean Wt increases slightly during the first 10 months of dialysis (Figure 3.2). Mean Wt is lower for non-survivors at month -12 and decreases sharply as the start of dialysis approaches. At month +1 following the start of dialysis survivors have a mean pre-dialysis Wt of 85 kg compared to 80 kg for non-survivors (Figure 3.2); no difference in slopes prior to dialysis initiation is observed

(Table 3.2). Absolute Wts are different for survivors versus non-survivors, but pre-dialysis start Wt slopes are not significantly different.

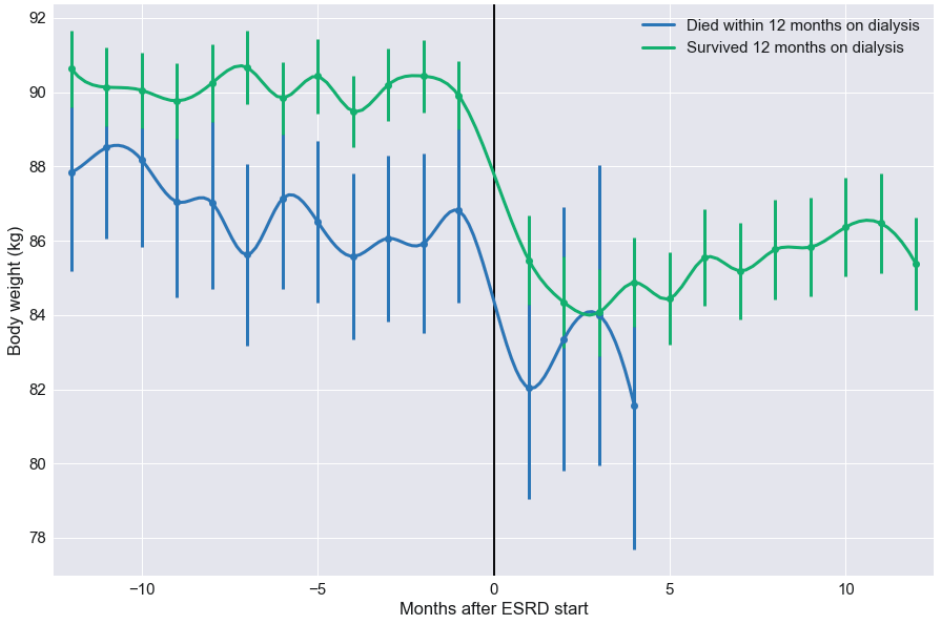

Figure 3.2 Wt in the 12 months before and after HD start for survivors and non-survivors.

Albumin

Mean serum albumin (Alb) decreases in the 12 months before dialysis start although the change is small at 0.01 g/dl/month (Table 3.2). Mean serum Alb rises in the first 4 months of dialysis and continues a slow and steady rise up to month +12 (Figure 3.3). Mean serum Alb begins to decline at 2 months before dialysis start (Month -2) for patients who do not survive the first 12 months on dialysis compared to patients who do survive the first dialysis year (Figure 3.3), although the slopes over 12 months are similar using simple linear regression (Table 3.2).

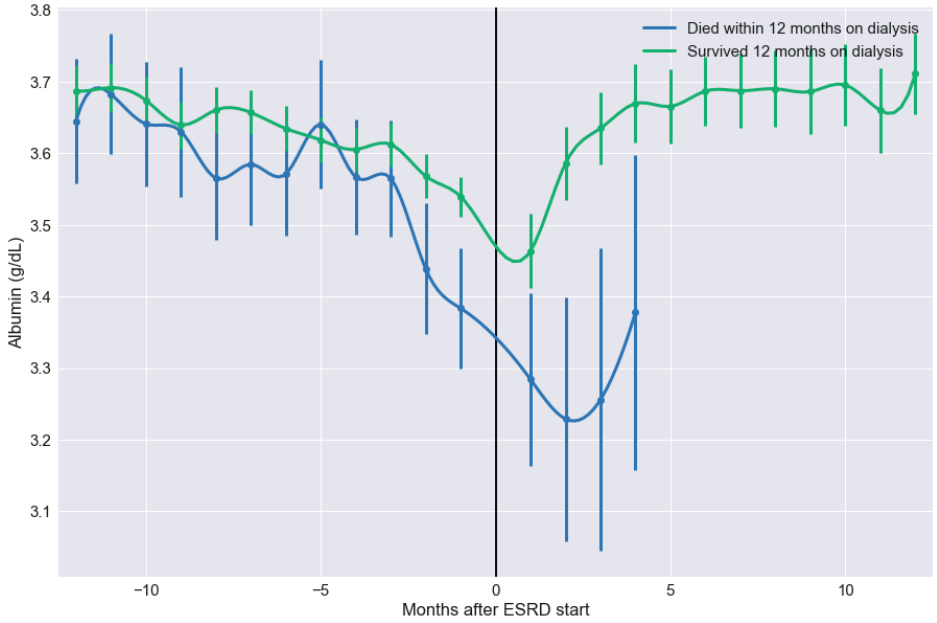

Figure 3.3 Alb in the 12 months before and after HD start for survivors and non-survivors.

White blood cell count

White Blood Cell (WBC) counts increase by 0.02 x 10^9/l/month from month -12 to dialysis start. Overall WBC counts decrease in the first 4 months of dialysis (Figure 3.4). In those who do not survive, WBC counts tend to be higher compared to survivors both during the 12 months before and the 4 months after dialysis start (Figure 3.4). The mean increase in WBC is higher in the patients who died than those who survived using simple linear regression (Table 3.2).

Sodium

Mean serum sodium (Na) is stable until month -2 when it declines. Mean serum Na further declines throughout the first 12 months of dialysis (Figure 3.5). On average non-survivors have a lower serum Na at month -12 compared to survivors. Non-survivors also experience a sharper decline in serum Na beginning at month -4, however, the difference in monthly changes in serum sodium is borderline significant in the 12 months prior to dialysis initiation (Table 3.2). During months +2 to +4 non-survivors have persistent mean serum Na of less than 138.5 mmol/l compared to survivors with mean serum Na of greater than 138.5 mmol/l (Figure 3.5).

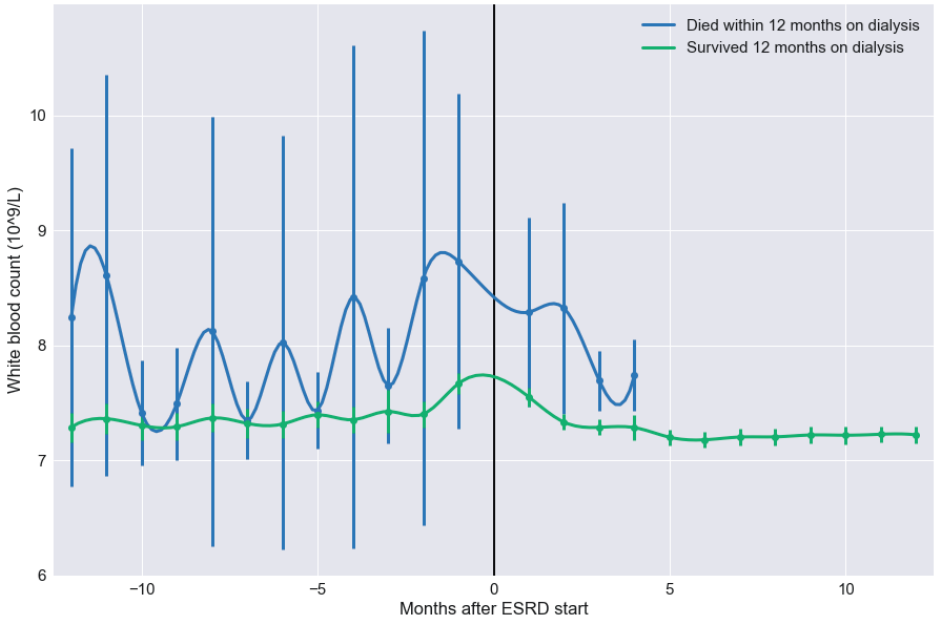

Figure 3.4 WBC in the 12 months before and after HD start for survivors and non-survivors.

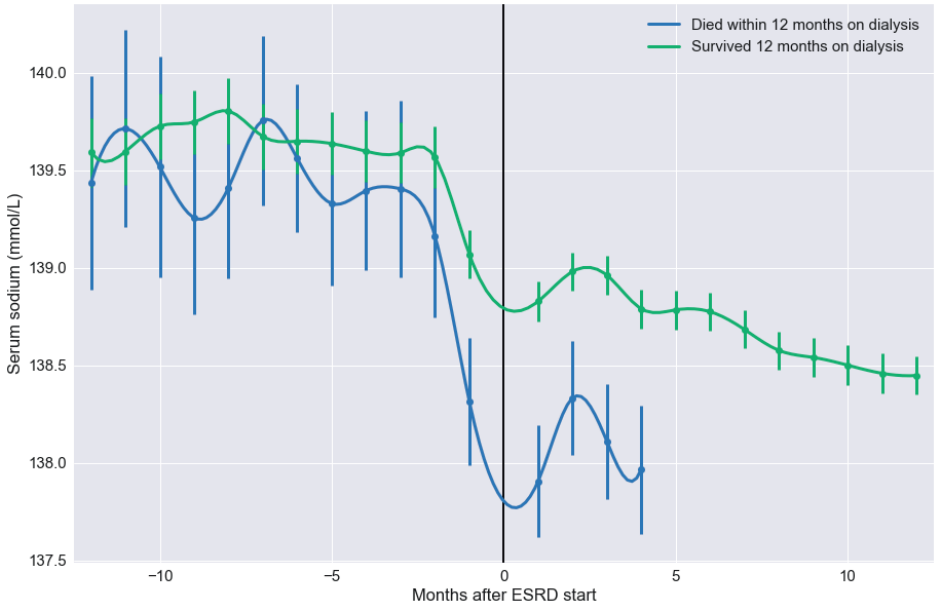

Figure 3.5 Na in the 12 months before and after HD start for survivors and non-survivors.

Phosphorus

Mean serum phosphorus (Phos) gradually rises in the 12 months before dialysis start by 0.07 mg/dl/month (Table 3.2). There is a decline in mean serum Phos at dialysis start and then Phos rises to stabilize by month +4 (Figure 3.6). Survivors and non-survivors have a similar mean serum Phos in the 12 months before dialysis start, but patients who survive have a higher mean serum Phos in the months after dialysis start (Figure 3.6).

eGFR

Mean eGFR declines in patients prior to dialysis initiation by 0.67 ml/min/month (Table 3.2, Figure 3.7). Survivors and non-survivors have similar rates of eGFR decline prior to dialysis initiation (Figure 3.7, Table 3.2).

In a separate analysis, we also compared rates of eGFR decline in different age groups, genders, and races. We observed that patients >65 years tend to decline significantly slower (monthly decline=0.63 ml/min/month) compared to patients ≤65 years (monthly decline=0.74 ml/min/month). No significant differences between genders was observed although white patients tend to decline significantly slower (monthly decline=0.61 ml/min/month) compared to black patients (monthly decline=0.80 ml/min/month).

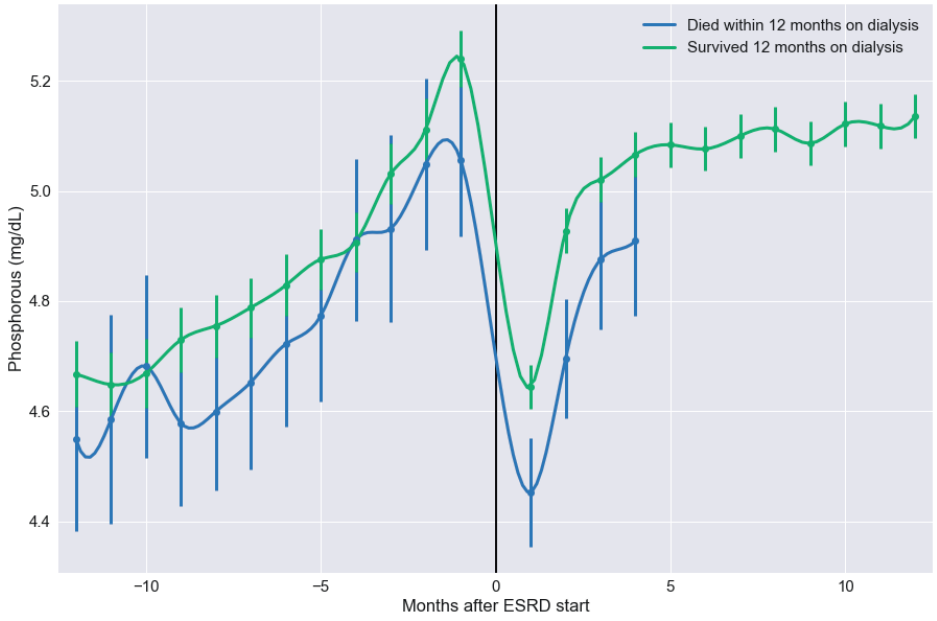

Figure 3.6 Phos in the 12 months before and after HD start for survivors and non-survivors.

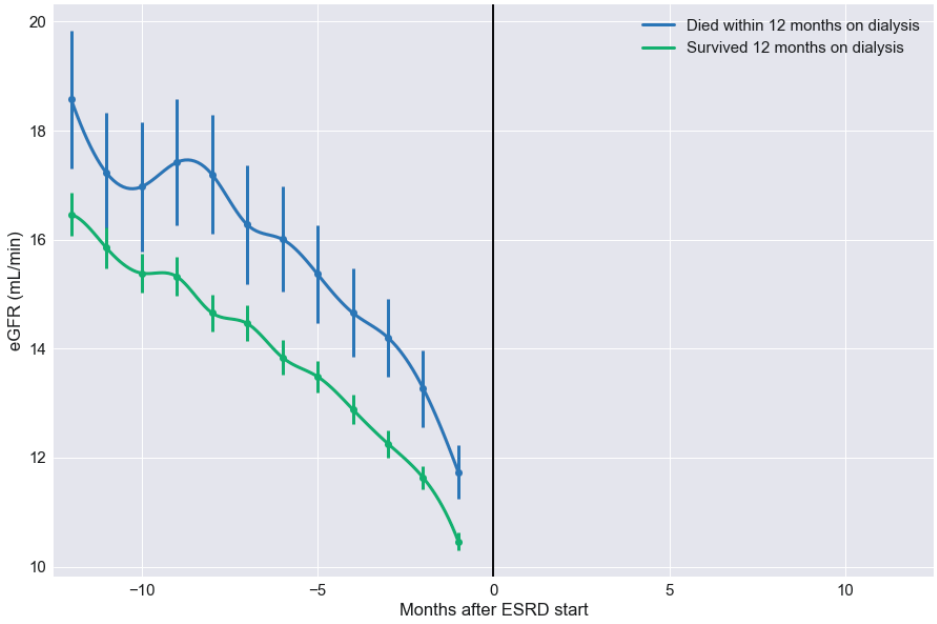

Figure 3.7 eGFR in the 12 months before and after HD start for survivors and non-survivors.

Discussion

In this study, we examine trajectories in clinical and laboratory parameters through the transition from the pre-dialysis to the dialysis phase during a 24-month period including 12 months before and after dialysis start. In the pre-dialysis phase, these parameters are compared between patients who did or did not survive the first year on dialysis in order to investigate whether trajectories of important outcome predictors diverge in the pre-dialysis phase. We chose these parameters because they are considered important markers for cardiovascular, nutritional, and inflammatory dimensions as well as mineral metabolism, which have been shown to be related to outcomes in previous studies.

Data linking the transition period from pre-dialysis to vintage dialysis are limited in patients with ESRD. To the best of our knowledge trajectories during the pre-dialysis phase comparing patients who survived or did not survive the first year on dialysis, have not been reported. Given the excess mortality in the early dialysis period,[2,6,7] identifying potentially modifiable parameters in the pre-dialysis phase may have important clinical relevance.

In this analysis SBP decreases after dialysis initiation and continues to decline until 4 to 6 months following the start of dialysis. A decline in SBP has been shown previously in European dialysis populations,[8-10] but is in some contrast to earlier observations in U.S. dialysis populations. From a pathophysiologic point of view, SBP is expected to decline following fluid removal after dialysis initiation. In previous studies, the use of high doses of erythropoietin might have caused adverse effects on BP control following the start of dialysis.[11,12] Since the present database covers a more recent time period compared to previous reports, lower doses of erythropoietin following FDA recommendations in 2012 might have uncovered the physiologic effects of fluid removal on SBP which were not apparent in previous studies. When comparing pre-dialysis trajectories in SBP between survivors and non-survivors, small differences were already observed in the first half of the year before the start of dialysis, although trajectories significantly diverged 3 months before the start of dialysis with a continuing diverging trend in the first months after the start of dialysis. This is in line with the strong relation between low SBP at dialysis start and outcomes.[9,10]

In this study the slope of SBP decline in the 12 months before dialysis start is significantly steeper for patients who do not survive the first 12 months of dialysis. The etiology of this cannot be determined from this study, but this may reflect impaired cardiac response to volume expansion. Patients with poor early dialysis survival may have underlying cardiovascular dysfunction with a lack of SBP rise in response to volume expansion with worsening renal function pre-dialysis start.

Regarding nutritional indices, Wt declines sharply following the start of dialysis, which is most likely related to removal of excess fluid, reaching a nadir 3 months after the start of dialysis followed by an increasing trend, which is generally in line with previous studies.[8,9] Average Wt was significantly lower 12 months before dialysis start in non-survivors versus survivors, but the slopes were not significantly different.

The increase in serum Alb following the start of dialysis is in line with previous studies.[13,14] However, to the best of our knowledge, the overall sharp decline in Alb levels before the start of dialysis has not previously been reported. The increase in Alb levels following the start of dialysis may be due to reversal of fluid overload as well as to improvement of appetite due to the partial reversal of the uremic state.[2] When comparing Alb trajectories between survivors and non-survivors, trends start to diverge around 3 months before the start of dialysis, closer to the time of transition to dialysis compared to trends for SBP although the slopes over the 12 months before dialysis start are not significantly different.

For the inflammatory dimension, WBC counts are used. Although a relatively crude index of inflammation, WBC counts have been found to be related to outcome in dialysis patients.[15] WBC increases before dialysis start and drops to baseline levels in the early dialysis or vintage period. There are several possible explanations for the increase in WBC count in the late pre-dialysis phase, such as the placement of central venous catheters[16] or the pro-inflammatory effect of fluid overload[17] or uremic toxins.[18]

Regarding the difference between survivors and non-survivors, WBC counts are generally higher in the non-survivor group, both in the pre-dialysis and in the vintage phase, but slopes of change in the pre-dialysis period are not significant.

Low serum Na levels are also important predictors of mortality in dialysis patients.[19] Na appears to be a composite parameter which, in addition to hydration, is also influenced by malnutrition and inflammation in ESRD patients.[20] In general, Na levels decline following the start of dialysis. The explanation for this observation remains hypothetical and might include effects of dialysate Na, although the relation between dialysate and serum Na levels remains controversial.[21] This cannot be further investigated in this study since dialysate. Na levels were not available. Trends in serum Na levels diverge 3 months before the start of dialysis between survivors and non-survivors, following a more pronounced negative trend in the latter group. The relation with malnutrition and inflammation discussed earlier may provide a potential explanation for this finding.

Increasing trends in serum Phos levels are observed pre-dialysis, followed by a sharp decline in the early dialysis period and a subsequent rise. In non-survivors, Phos levels in the pre-dialysis phase are, in general, lower which may be explained by lower protein intake in this group, but the slope of Phos change is not significantly different.

The overall trajectory of eGFR shows the expected decline in the 12 months pre-dialysis start. Our findings are consistent with prior studies showing that patients with steeper eGFR trajectories in the 24 months before dialysis start are less likely to receive pre-dialysis nephrology care and are less likely to survive the first year of dialysis.[22]

Whereas clear trends could be observed, limitations of this analysis are that only de-identified data is used. Also, this analysis only includes patients who have received outpatient CKD care in a nephrology practice during the 12 months before dialysis start which restricts generalization to patients who start dialysis without prior nephrology care or as the result of an acute renal failure event. Moreover, in the figures, aggregated means are reported during each month since data are not always available for all patients on a monthly basis. We also note that due to limitations of clinical parameters collected in the CKD registry we use WBC count as a crude marker of inflammation. However, all prognostic parameters addressed in the present study are already significantly different between survivors and non-survivors in the pre-dialysis phase. Given these limitations, we suggest that our results should be considered as hypothesis generating.

This observational data suggests that patients with similar clinical parameters at 12 months before dialysis start may begin to show a divergence in clinical trajectories in the several months just before dialysis start that are associated with increased post dialysis start mortality. Given the observational nature of this study, it is not clear that the trajectories apparent in the CKD pre-dialysis course are amenable to therapeutic intervention or that dialysis outcomes can be changed, but this divergence may enable early identification of high risk incident dialysis patients. It is notable that the observed

differences in parameters between survivors and non-survivors are, apart from SBP and serum albumin levels, mostly small in absolute terms.
In summary, this paper shows important trends in prognostic parameters in ESRD patients, both in the pre-dialysis as well in the dialysis or vintage phase. Some clinical parameters begin to diverge before the start of dialysis and may represent a 'window of opportunity' to intervene to change patient outcomes after the start of dialysis. The pre-dialysis phase offers additional targets for early intervention and possible development of predictive models for patient outcomes.

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Chapter 4

Effects of renal care coordinator case management on outcomes in incident dialysis patients

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Abstract

Background

Pre-dialysis chronic kidney disease (CKD) care impacts dialysis start and incident dialysis outcomes. We describe the use of late stage CKD population data coupled with CKD case management to improve dialysis start.

Methods

The Renal Care Coordinator (RCC) program is a nephrology practice and Fresenius Medical Care North America (FMCNA) partnership involving a case manager resource and data analytics. We studied patients starting dialysis between Aug 1, 2009 and Feb 28, 2013 in 9 nephrology practices partnering in the RCC program. Propensity score matching (PSM) was used to match patients who had participated in the RCC program to patients who had not.

Primary outcomes were use of a permanent access or peritoneal dialysis (PD) at first outpatient dialysis. Serum albumin at the first outpatient dialysis treatment and mortality and hospitalization rates in the first 120 days of dialysis were secondary outcomes.

Results

In the nephrology practices studied, 7626 patients started dialysis. Of these, 738 patients (9.7%) were enrolled in the RCC program; 693 RCC patients (93.9%) were matched with 693 patients who did not participate in the RCC program. Logistic regression analysis indicates that RCC program patients are more likely to start PD or use a permanent vascular access at dialysis start and are more likely to start treatment with a serum albumin level ≥4.0 g/dl.

Conclusion

Late stage CKD data-driven case management is associated with a higher rate of PD use, lower central venous catheter (CVC) use, and higher albumin levels at first outpatient dialysis.

Introduction

Late stage CKD patients benefit from treatment options education and a stable transition to dialysis with reduced short and long-term dialysis morbidity and mortality.[1-6] Previous studies and reviews have documented key practices in preparing patients for an ideal or optimal dialysis start.[3,4] In 2012 Saggi, et. al. noted that an ideal start for dialysis includes avoiding uremia-related hospitalizations, good education about treatment options, and functioning permanent access placement prior to dialysis initiation.[3] Despite awareness of the improved outcomes associated with an ideal dialysis start, most patients, even those with long-term nephrology care, do not start dialysis with a functioning permanent access.[7]

Pre-dialysis multidisciplinary care that includes disease-specific patient education, use of standard protocols for patient management, and coordination of care improves CKD outcomes compared to standard nephrology care.[8-12] CKD programs that involve multidisciplinary care teams and case management strategies have been successful in improving CKD outcomes.[8,9,11,13]

Despite timely referral to nephrologists, patients with CKD who start hemodialysis (HD) with a CVC are at increased risk for hospitalization and death during the first year of dialysis.[4,14] Mortality in incident dialysis patients is especially pronounced in the first 120 days after the start of dialysis, a phenomenon in which modifiable pre-dialysis treatment related factors likely play an important role.[15]

Patient characteristics at the start of dialysis and patient outcomes during the incident dialysis period are a reflection of the care patients receive during late stage CKD (CKD stages 4 and 5).[4,6] Data-driven late stage CKD management results in an improved dialysis start.[16] Patients have a greater likelihood of having an “optimal start” to dialysis (e.g. dialysis initiation as an outpatient with use of a permanent access at first outpatient dialysis) if treatment options education, modality selection and timely creation of a usable permanent access are provided in the months prior to starting dialysis treatment.[2,4,16] In particular, CKD education is associated with permanent access use and an outpatient planned start at first dialysis as well as an increased use of home therapies.[2,17] Despite exposure to standard CKD education many patients who start dialysis still have inadequate knowledge about treatment options and the details of dialysis treatment.[17]

We report the results of the RCC program which is a structured CKD program with CKD case managers and analytical tools in the nephrology practice. This data-driven case management intervention focuses on treatment options education, modality selection, usable permanent access placement, and an “optimal” outpatient start to dialysis.

Materials and methods

RCC program description

The RCC program is a partnership between nephrology practices and FMCNA that is geographically diverse and spans a variety of nephrology practice models. This program has two major components: a case manager resource embedded in the nephrology practice and centralized data analytics. The program is focused on CKD education, modality selection, usable permanent access placement (arterio-venous fistula or graft, peritoneal dialysis catheter), and an outpatient start to dialysis.

Patients who are not in the RCC program are cared for in the usual workflow of the nephrology practice. Non-RCC patients attend CKD education as directed by the nephrologist. Modality selection is made with the support of the nephrologist and orders for and management of permanent access preparation is overseen by the nephrologist.

The RCC case manager, who has a clinical background as a licensed practical nurse (LPN), registered nurse (RN) or family nurse practitioner (FNP) with renal experience, is a shared resource between the nephrology practice and FMCNA. The embedded case manager works within the local culture of the practice to coordinate CKD education and permanent access resources for enrolled patients. Patients are actively managed by the RCC when the estimated glomerular filtration rate (eGFR) is less than 30 ml/min/1.73m^2 and until the patient begins dialysis. In some practices an eGFR of less than 30 ml/min/1.73m^2 automatically generates referral to the RCC program that can be over-ridden by the nephrologist. In other practices the 30 ml/min/1.73m^2 triggers a request to the nephrologist for enrollment in the RCC program. In the case of some large nephrology practices with multiple clinic locations, the RCC program may not be present in all clinic locations, however, all practice locations meet a similar standard of care delivery for the practice as a whole. RCC enrollment is outlined in Figure 4.1.

The RCC program includes data reporting created from the integration of limited nephrology practice business data, nephrology practice clinical electronic health record (EHR) data, and FMCNA's clinical database. This integrated data creates a detailed late stage CKD patient "inventory" for the RCC enabling CKD patient population management and providing a weekly workflow report for the RCC case manager. Reports show process metrics for CKD education, modality selection, and permanent access placement for patients who are enrolled. While RCC case management ceases at the start of dialysis, data analytics and reporting extend into the first 120 days of dialysis to create outcomes metrics on hospitalizations, missed HD treatments, 120 day mortality, and access type for all new dialysis starts within the practice.

RCC CKD education is based on requirements outlined in the Medicare Improvement for Patients and Providers Act (MIPPA)[18] which includes comprehensive information about co-morbidity management, strategies to slow CKD progression, prevention of

uremic complications, and treatment options for renal replacement therapy. Non-RCC patients may receive CKD education from the nephrology practice or from other treatment options education programs.

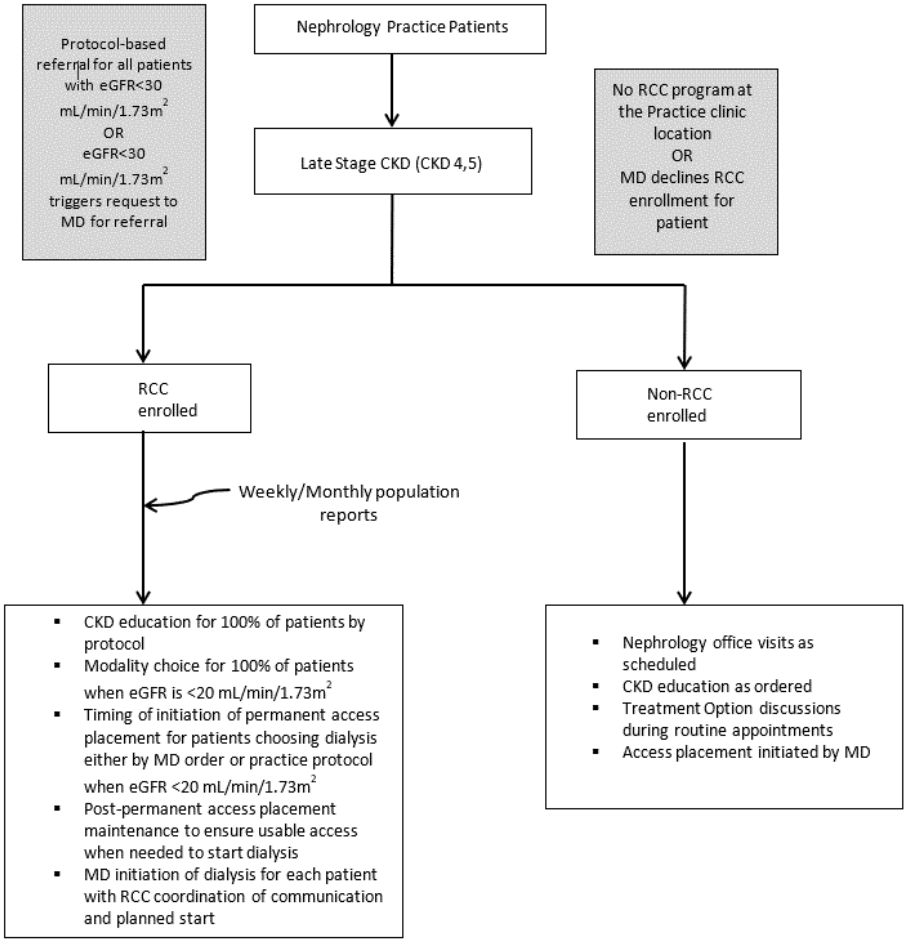

Figure 4.1 RCC program overview.

RCCs foster shared decision making in treatment option selection which may include dialysis, renal transplantation, or conservative management. Patients who choose renal transplantation receive referral assistance to a renal transplant center. Patients who choose conservative management receive support for this care through the nephrologist. For patients who plan to start dialysis, a process is initiated at the

appropriate time to create a permanent peritoneal or vascular access that is usable and maintained until the start of dialysis.
RCC program patients continue to receive CKD education and case management until the start of dialysis. RCCs do not provide direct patient care for co-morbidities, but may coordinate this care if patients have complaints or concerns. RCCs do not provide direct care for CKD complications such as anemia or phosphorus control, but provide coordination of care if interventions are needed. Patients continue to receive care from nephrologists while receiving RCC case management support.

Data sources and study population

To determine the association of RCC program and incident dialysis patient outcomes, we studied all patients who transitioned to end stage renal disease (ESRD) between Aug 1, 2009 and Feb 28, 2013 in the 9 nephrology practices participating in the RCC program. Any patients receiving RCC case management contact after the first day of work of the RCC is considered an RCC program enrollee. Patients enrolled in the RCC program may start dialysis within weeks of RCC program enrollment as the RCC begins work in the nephrology practice.
For each patient, we noted modality, access type, and level of serum albumin at the first outpatient dialysis treatment. Hospital admission, hospitalization days, and mortality rates in the first 120 days of dialysis were computed. Analysis included patients starting with in-center HD and PD. Laboratory results in the FMCNA database are automatically downloaded from Spectra Laboratories (Rockleigh, NJ). Hospitalization data is recorded by the dialysis clinic staff and is based on the communication with the patient, patient's nephrologist, and discharge summaries, when available. The study was conducted in compliance with local rules and regulations to protect data privacy and patients' rights.

Statistical analysis

Data are presented as mean and standard deviation (SD) for continuous variables and percent (%) for categorical variables. T-tests were used to compare continuous and categorical variables.
We employed 1:1 PSM to balance pre-dialysis covariates between RCC program enrollees ("cases") and control patients. PSM was conducted using the following covariates: nephrology practice; patient age, gender, race (Caucasian/non-Caucasian), diabetes status, length of pre-dialysis care in the respective practice, payor type (including Medicaid, Medicare, commercial and self-pay) and calendar year of dialysis initiation.
Logistic regression analyses adjusted for age, gender, race, ethnicity, diabetic status, time in practice and year of dialysis start were used to compute the odds ratio of death

as well as starting with PD modality, CVC as primary vascular access, and serum albumin ≥4.0 g/dl, respectively. Poisson regression was employed to compare hospitalization rates with the log of exposure days as the offset variable adjusted for age, gender, race, ethnicity, diabetic status, time in practice, and year of dialysis start. All p-values are two-sided. The analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC) except PSM which was performed using optimal matching in R-software version 3.1.1, MatchIt add-on.

Results

In 9 nephrology practices 7626 patients started dialysis; 738 (9.7%) were enrolled in the RCC program and 6889 (90.3%) were not. Based on Kaplan-Meier analysis time to first outpatient Fresenius dialysis, the median for the RCC group was 3 days (95% CI 2 to 5 days) and the median for the non-RCC group was 7 days (95% CI 6 to 8 days) as shown in Figure 4.2. The logrank test showed that patients in the RCC program started dialysis as an outpatient significantly sooner as compared to the non-RCC group (p<0.0001)

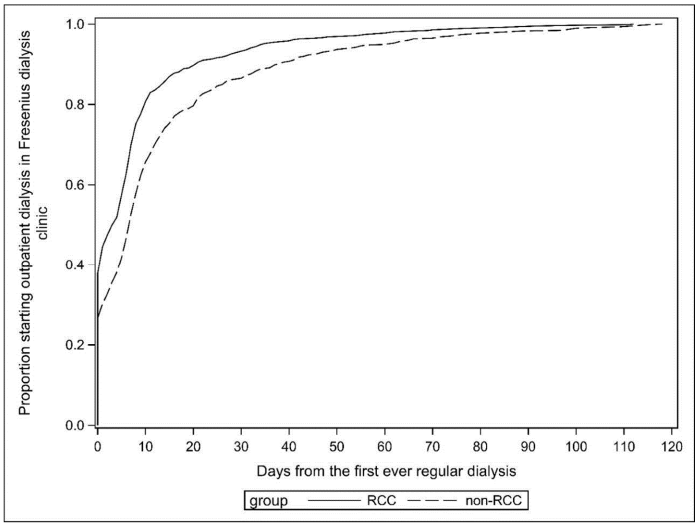

Figure 4.2 Kaplan-Meier time to first outpatient Fresenius dialysis from first ever chronic dialysis.

In 45 RCC patients variables required for PSM were missing; consequently, 693 RCC patients (93.9%) were successfully matched with 693 non-RCC patients. The characteristics of RCC patients and their matched controls are shown in Table 4.1. While age was comparable (cases 63.1 years; controls 64.0 years), patients in the RCC

program were less likely to be white (66% versus 69%), less likely to be Hispanic (8% versus 13%), and had spent more time under the care of the respective nephrological practice (33 versus 31 months).

Table 4.1 Pre-dialysis characteristics of RCC enrollees and propensity score matched control patients.

	RCC enrollees (N=693)	Controls (N=693)	Absolute difference (95% CI)	p-value
Age	63.1 (13.4)	64 (14.5)	0.9 (-0.4 to 2.3)	
Male (%)	56.60%	59.20%	2.6 (-2.7 to 7.4)	
White (%)	65.80%	68.70%	2.9 (-1.8 to 7.7)	
Hispanic (%)	7.80%	13.30%	5.5 (2.1 to 8.6)	
% Diabetic	62.80%	62.20%	-0.6 (-5.2 to 4.3)	
Number of months in the practice	24.1	25.8	1.7 (-4.1 to 0.8)	
Deaths in first 120 days (per 100 py)	8.55	6.93		0.5025
Hospital admissions in first 120 days (ppy)	1.28	1.5		0.0483
Hospital days in first 120 days (ppy)	8.9	11.5		<.0001
Starting with PD modality (%)	24.10%	15.20%	-8.9 (-13.5 to -4.5)	<.0001
CVC at start (%)	42.40%	64.50%	22.1 (16.8 to 27.7)	<.0001
Albumin≥4.0 g/dl at dialysis start (%)	27.60%	20.30%	-7.3 (-12.1 to -3.2)	0.0024

Unadjusted logistic regression analysis indicated no difference in mortality rates between cases and controls (8.6 versus 6.9 per 100 patient years, p=0.503). RCC patients had a higher PD use as first treatment modality (24.1% versus 15.2%, p<0.001), had less frequently CVCs as usable vascular access (42.4% versus 64.5%, p<0.001), and were more likely to start dialysis with serum albumin levels ≥4.0 g/dl (27.6% versus 20.3%, p<0.001). Both hospital admissions and hospital days were lower in the RCC group (1.3 versus 1.5 per patient year, p=0.0483, and 8.9 versus 11.5 per patient year, p<0.001). Results of adjusted logistic regression are presented in Figure 4.3.

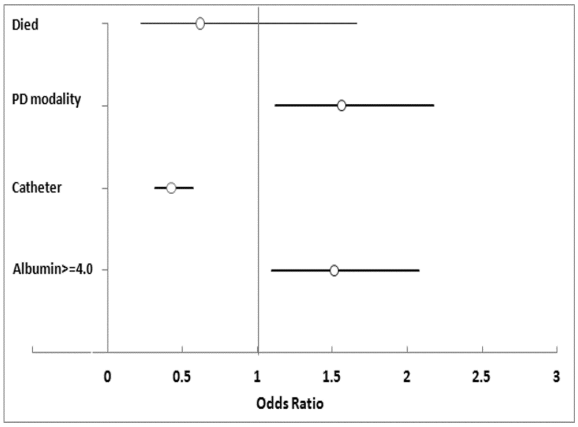

Figure 4.3 Adjusted odds ratio of death in the first 120 days, starting with PD modality, CVC, and albumin≥4.0, respectively, for patients in the RCC program compared to controls.

Discussion

This study suggests that RCC case management deployed in late stage CKD is associated with a higher rate of PD as first treatment modality, a lower rate of CVCs as primary vascular access, and higher albumin levels at first outpatient dialysis. Moreover, in the RCC program a decreased time to chronic dialysis treatment as an outpatient was observed.

RightStart and other programs report that education, nutrition, adequacy, and anemia management at dialysis start are associated with decreased morbidity and mortality.[19] Canadian studies report the impact of multidisciplinary pre-dialysis CKD care on morbidity and mortality in the first year of dialysis.[10] This paper adds to the body of knowledge on the impact of pre-dialysis education and support for modality selection and permanent access placement on the use of a permanent access and PD at the first outpatient dialysis treatment in U.S. patients.

Patients enrolled in this data-supported case management program are more likely to start dialysis on PD or to start HD with a permanent access compared to patients not in the RCC program. Albumin at the start of HD or PD tends to be higher for the RCC enrollees. This may relate to improved CKD and nutrition education by RCCs, but may also be related to elective placement of a permanent access before dialysis start.

Patients who receive RCC management tend to have fewer hospital admissions and hospital days in the first 120 days of dialysis compared to their peers who receive usual CKD care in the same practice. Previous studies demonstrate that multidisciplinary CKD care increases the likelihood of an improved dialysis start although it is not known what interventions are most important. This study of data-supported case management of late stage CKD patients within the nephrology practice is focused on modality selection and permanent access management for patients with an eGFR <30 ml/min/1.73m^2.

High CVC use at the start of HD is often attributed to late nephrology referral, but patients in the U.S. who receive standard nephrology care also have high CVC rates.[7,10] Even patients who receive care in a nephrology practice for greater than 12 months prior to dialysis initiation too often have a "suboptimal" start to dialysis.[4,16,20] A "suboptimal" dialysis start (an unplanned start in the hospital with a temporary catheter) is associated with poorer patient outcomes in the first year of dialysis.[4]

A recent Canadian study demonstrated that "cumulative" nephrology care (number of visits in the 12 months before dialysis), and "consistent critical period" care (care in the 6 months before dialysis start) are associated with decreased mortality in the first year of dialysis.[5] "Cumulative" care and "consistent critical period" care are associated with an increased likelihood of the creation of a pre-dialysis access.[5] Late stage CKD case management, as in this study, that is focused on population management may improve the likelihood of both cumulative care overall and critical period care in particular.

Starting HD with a permanent access is associated with lower morbidity and mortality. In a recent report by Chan, et al, patients in the first 90 days of dialysis had relative risks

of death of 2.16 and of hospitalization of 1.51, relative to patients who have survived the first year of dialysis.[21] Permanent vascular access and albumin levels ≥4 g/dl were associated with better patient survival in the Chan study. Patients starting with a CVC had a twofold mortality risk even when controlled for comorbidities and mortality-associated confounders.[21]

Nephrology practice claims and clinical data provide an opportunity for CKD population management through identification and tracking of late stage CKD patients. However, it may be very difficult to scale case management resources to manage an entire late stage CKD population within a practice. More research is required to identify patients who are likely to start dialysis within the next 6 to 12 months to help to focus dialysis preparation resources where they are most needed.

Even with case management to support timely permanent access creation, it is difficult to obtain and maintain a permanent access that is successfully used at the first dialysis. Surgical outcome data and improved planning for the best permanent access for every individual patient remain important issues.

Physician-specific data on late stage CKD care may change physician practice patterns. Physician "Report Cards" with late stage CKD patient outcomes and data on "suboptimal" dialysis starts may change physician behavior with regard to CKD education and timely referral for permanent access placement. Such "Report Cards" allow physicians to benchmark their patient outcomes against those achieved by peers within the same practice.

While the large number of patients adds strength to this study, there are obvious limitations. First, the study was designed as an observational trial. While highly desirable, logistic considerations prevented a random allocation of late stage CKD patients to the RCC program or standard care, respectively. Instead, patients were allocated at the discretion of the nephrologist. This deficit may have resulted in a preferred allocation of patients to one arm or the other and thus imbalances with respect to unmeasured covariates may exist. In recognition of this limitation we employed 1:1 PSM to balance key covariates between RCC enrollees and controls. Admittedly, despite these efforts the existence of residual confounding cannot be ruled out. Second, it is possible that the presence of the RCC program in the nephrology practice influenced the management of non-RCC patients. Non-RCC patients may have benefitted from the enhanced awareness of CKD care by all nephrology practice providers which would suggest that the outcome differences between RCC and non-RCC patients may be more pronounced than reported here. Third, we had no access to follow-up data of patients who opted for either pre-emptive renal transplantation or conservative management without dialysis. Therefore, these important patient groups are unaccounted for in the current analysis.

Conclusion

Our results indicate that a data-driven case management program, such as the RCC program, is associated with a greater likelihood of improved dialysis start and outcomes in the first 120 days on dialysis. Patients enrolled in the RCC program are more likely to start on PD or to start HD with a permanent access. During the incident dialysis period we observed a trend towards fewer hospital admissions and hospital days in RCC enrollees. This study suggests that late stage CKD patient case management focused on CKD education, modality selection, and usable permanent access placement and management increases the likelihood of an improved dialysis start and incident dialysis outcomes.

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Chapter 5

Transition period clinical trajectories for PD versus HD starters

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Abstract

Background

Peritoneal dialysis (PD) starters generally have a better outcome compared to hemodialysis (HD) starters perhaps related to treatment characteristics or case-mix. We previously showed that pre- and post-dialysis start clinical parameter trajectories are related to outcomes. The aim of this study was to investigate these trajectories in PD and HD starters.

Methods

This retrospective observational study analyzing data from the Fresenius Medical Care-CKD Registry from 1/2009 to 3/2018 examines trends in key clinical parameters through the transition period covering 12 months before to 12 months after dialysis start in 8088 HD and 1015 PD starters.

Results

HD starters differed from PD starters by a significantly greater decline in eGFR slope (-0.64 vs. -0.45 ml/min/1.73m^2/month) before and higher eGFR (9.85 vs. 7.84 ml/min/1.73 m^2) at dialysis start. Relatedly, differences in phosphorus (0.07 vs. 0.05 mg/dl/month) and hemoglobin (-0.08 vs. -0.01 gm/dl/month) slopes before the transition to dialysis therapy were observed. After dialysis start HD starters experienced a greater increase in albumin (0.01 vs. 0 g/dl/month) whereas PD starters experienced a decline in serum sodium and higher white blood cell counts compared to HD starters.

Conclusion

For nephrology practice CKD patients, HD and PD starters appear clinically comparable in the year before dialysis start although HD starters exhibit a more rapid pre-dialytic eGFR decline. Ideally, studies comparing incident HD and PD outcomes should also consider CKD eGFR trajectories. In the first dialysis year divergence occurs in albumin, white blood cell count, sodium and hemoglobin trends, which may be partly treatment related.

Introduction

Peritoneal dialysis (PD) is generally associated with improved patient outcomes in the first years after dialysis start[1-3] compared to hemodialysis (HD), although not all studies found this difference[4] while some authors attributed differences to case mix.[5,6]
In defining case-mix between PD and HD starters, usually parameters are collected at dialysis start, however, the relevance of pre-dialytic trajectories in predicting outcomes after dialysis start has been shown.[7-9] Recently, United States Renal Data System (USRDS) published data regarding medication use and hospitalization patterns through the transition to dialysis start, but obtaining continuous insight into pre- and post-dialysis start clinical and laboratory trajectories is generally difficult due to data collection in discontinuous databases.[10] Identifying different trajectories in the pre-dialytic period in PD vs. HD starters may have relevance for the design of future studies comparing early outcomes between both techniques.
In addition, PD and HD are associated with completely different treatment profiles which may have major influences on trajectories of important physiological and laboratory parameters and early dialysis outcomes. Since PD is a continuous technique, differential changes in body weight (Wt) and systolic blood pressure (SBP) may be expected after dialysis start compared to HD, whereas, due to protein loss in the dialysate, a less rapid increase in serum albumin (Alb) levels might be expected. However, until now, it has not been studied whether pre- and post-dialysis start trajectories of these parameters are indeed different between patients starting with either HD or PD. The same holds true for parameters in other domains, such as mineral metabolism and inflammation.
The aim of the present study was to compare trajectories of key clinical and laboratory parameters at 12 months before dialysis initiation, changes in parameters throughout dialysis start with either PD or HD, and changes through the first year of dialysis treatment. For this study, we analyzed de-identified Fresenius CKD Registry data from U.S. nephrology practices that is continuous from chronic kidney disease (CKD) through dialysis initiation over the 12 months pre- and post-dialysis start.

Methods

The Fresenius Medical Care-CKD Registry includes data for over half a million patients with CKD or end stage renal disease (ESRD) geographically dispersed in the U.S. who receive care from nephrology practices utilizing the nephrology-focused electronic health record (EHR). The Registry conforms to Safe Harbor de-identification standards; no identifying data are harvested, and all event dates are represented by a year and the number of days since the patient had an initial encounter in the nephrology office, which is stored outside the registry for data validation purposes. Data elements

including demographics, vital signs, lab results, and eGFR (calculated using the CKD-EPI and/or MDRD4 equation) are placed in the Registry. After IRB review this research was determined to not require IRB approval.

All clinical data reported originates in a nephrology-focused EHR used by providers in 39 U.S states and Puerto Rico. Post-dialysis start laboratory data are collected during dialysis treatments as part of routine testing and are imported into the nephrology practice EHR. De-identified data collected in the EHR are swept into the Fresenius Medical Care-CKD Registry on a weekly basis creating a large CKD database. Thus, the Fresenius Medical Care-CKD Registry represents a clinical data repository that remains intact through the transition from late stage CKD to ESRD.

For this analysis, data were included on all CKD patients seen between 1/2009 and 3/2018 as a CKD stage 1 to 5 patient in the 12 months before dialysis start and as an ESRD patient for the 12 months after dialysis start. The first date of chronic dialysis treatment was the date when a patient first received outpatient HD or PD treatment or first inpatient dialysis treatment that was immediately followed by outpatient dialysis therapy. Patients' initial dialysis modality was assessed based on the first outpatient dialysis treatment. Although data are not available for sub-modality determination, over 80% of Fresenius Kidney Care (FKC) PD patients are on an automated PD prescription with less than 20% on CAPD. During the study period from 2009 to 2018 less than 4% of FKC PD patients were prescribed icodextrin dialysate, so PD patients were mostly receiving dextrose-containing dialysate fluid. The majority of incenter FKC HD patients receive nephrologist prescribed HD with a hollow fiber high-flux membrane. No incenter HD patients were receiving hemodiafiltration.

Post-dialysis start laboratory data were collected as part of routine dialysis treatment monthly testing. Based on policies and procedures incenter HD laboratory specimens are all drawn pre-dialysis most often during the early week dialysis session such as Monday or Tuesday. In general, PD monthly labs are routinely drawn during the first 2 weeks of the month during a nurse visit. All clinical data were collected from the nephrology practice EHR.

A patient's initial dialysis modality was used in all intention-to-treat analysis. Supplemental analysis was also conducted for an as-treated analysis to examine outcomes for patients who remained on their starting modality throughout the first 12 months of dialysis treatment. Additional analysis included study of an intention-to-treat cohort matched on age and presence of diabetes mellitus (DM).

The present study includes selected parameters in the cardiovascular, nutritional, and inflammatory domains as well as mineral metabolism. Patient blood pressure (BP) and Wt were assessed only in the nephrology office both in pre-dialysis CKD care and after dialysis initiation. For each patient, laboratory and clinical data in monthly intervals before and after dialysis initiation were averaged.

Parameters were compared throughout 12 months before dialysis initiation, as well as at the time of initiation and throughout 12 months after dialysis initiation. In addition,

slopes of changes in patient parameters were computed for each laboratory and clinical parameter during the 12 months before dialysis initiation as well as after dialysis initiation using simple linear regression per patient. Linear Mixed Effects Model analysis was performed with similar findings, so this analysis is not presented here. Parameters at the different time points were compared using unpaired t-tests. Parameters and slopes were compared for patients starting dialysis using the different modalities, both as intention-to-treat and as-treated analyses. Lastly, parameters and slopes were compared for patients in the different treatment groups matched for age and diabetes.
Graphs for selected parameters at monthly time points are presented. Each point on the graph shows the mean value for that parameter across patients, with the error bars displaying the standard error of the mean. The smoothed line connecting the points is an interpolated spline fit generated using the Python package SciPy (https://www.scipy.org/citing.html). The plots themselves are generated using Matplotlib (Hunter, 2007 http://ieeexplore.ieee.org/document/4160265/?reload=true).
SAS version 9.3 (Cary, NC) software was used for statistical analysis.

Results

Patient characteristics

This study included 9103 patients, of which 8088 (89%) started dialysis with HD and 1015 (11%) with PD. In the year following dialysis start, 518 (6%) patients switched treatment modality (Figure 5.1). Patients starting PD, both in the intention-to-treat and the as-treated analyses were significantly younger and less likely to have DM, whereas gender and race did not differ (Table 5.1, Supplementary Table S5.1, Table 5.2). The number of data entries for each parameter per patient before and after the transition to start dialysis therapy is provided (Supplementary Table S5.2).

Pre-dialytic values and slopes

In the intention-to-treat analysis, at 12 months before dialysis start, most parameters did not significantly differ between HD and PD starters, except for small differences in SBP (143.35±19.750 vs. 141.58±18.258 mmHg; p=0.010) (Table 5.1). eGFR 12 months before dialysis start was significantly higher in HD vs. PD starters (15.55±7.7 vs. 11.64±6.10 ml/min/1.73m^2; p<0.001) and phosphate (Phos) (4.63±1.02 vs. 4.84±1.04 mg/dl; p<0.001) (Table 5.1).
Parameter slopes in the 12 months before dialysis start showed a more pronounced eGFR decline in HD vs. PD starters (-0.64±0.77 vs. -0.45±0.54 ml/min/1.73m^2/month; p<0.001) (Table 5.1). HD starters also experienced a significantly larger decline in hemoglobin (Hgb) and corrected calcium (Ca) and a larger increase in serum Phos (Table 5.1).

Pre-dialysis results did not materially change in an as-treated analysis (supplementary Table 5.1) and when matched for age and diabetes (Table 5.2).

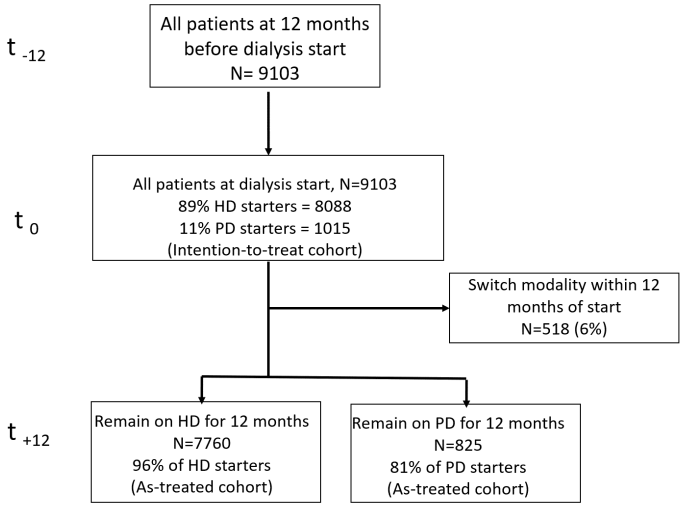

Figure 5.1 Study flow chart.

Parameters at dialysis start, at 12 months after dialysis start, and post-dialysis start slopes

At dialysis start the intention-to-treat analysis showed that Hgb levels were significantly lower (10±1.32 vs. 10.60±1.39 g/dl; p<0.001) whereas SBP levels (144.53±19.94 vs. 141.08±19.01 mmHg; p<0.001) and Wt tended to be higher (89.96±25.5 vs. 88.24±22.79 kg; p=0.06) in HD vs. PD starters. eGFR was significantly higher in HD compared to PD starters (9.85±4.13 vs. 7.84±3.21 ml/min/1.73m^2; p<0.001). The other parameters did not differ significantly (Table 5.1).

After dialysis initiation, slopes for Hgb (more positive in HD starters), serum sodium and Alb (more negative in PD starters), and white blood cell (WBC) count (more positive in PD starters) were significantly different between both groups (Table 5.1).

Twelve months after dialysis start, Alb levels were significantly higher in HD starters (3.81±0.35 vs. 3.54±0.42 g/dl; p<0.001) and WBC counts (7.06±2.51 vs. 7.68±2.67 * 10^9/l; p<0.001) and Wt (84.58±24.1 vs. 87.73± 23.56 kg; p<0.008) were significantly lower compared to PD starters (Table 5.1). In the as-treated analysis (supplementary Table 5.1), results were not materially different. The same held true for the comparison between both groups when matched for sex and diabetes, except for a small difference in Phos between HD and PD starters at the different time points and an absence of differences in Wt 12 months after dialysis start.

Table 5.1 Demographics and pre-dialysis trajectories as intention-to-treat.

	HD Starters	PD Starters	p-value
Number of patients	8088	1015	
Black race, %	25%	24%	0.337
Male, %	56%	56%	0.769
Diabetes mellitus, %	58%	47%	0.000
Married, %	39%	43%	0.012
Age, years	64.15 (12.92)	58.99 (14.11)	<0.001
Albumin at t_{-12}, g/dl	3.69 (0.46)	3.7 (0.45)	0.679
Corrected calcium at t_{-12}, mg/dl	8.99 (0.67)	8.97 (0.67)	0.639
Hemoglobin t_{-12}, g/dl	10.72 (1.45)	10.81 (1.45)	0.092
Phosphorus t_{-12}, mg/dl	4.63 (1.02)	4.84 (1.04)	<0.001
Sodium t_{-12}, mmol/l	139.78 (3.02)	139.7 (3.05)	0.456
WBC t_{-12}, $*10^9$/l	7.39 (2.74)	7.46 (2.17)	0.445
eGFR t_{-12}, ml/min/1.73m^2	15.55 (7.7)	11.64 (6.1)	<0.001
SBP t_{-12}, mmHg	143.35 (19.75)	141.58 (18.25)	0.010
Weight t_{-12}, kg	91.04 (24.9)	89.52 (23.44)	0.092
Albumin slope t_{-12} to t_0, g/dl/mo	-0.01 (0.05)	-0.01 (0.06)	0.576
Corrected calcium slope t_{-12} to t_0, mg/dl/mo	-0.02 (0.09)	0 (0.09)	<0.001
Hemoglobin slope t_{-12} to t_0, g/dl/mo	-0.08 (0.18)	-0.01 (0.2)	<0.001
Phosphorus slope t_{-12} to t_0, mg/dl/mo	0.07 (0.17)	0.05 (0.17)	<0.001
Sodium slope t_{-12} to t_0, mmol/l/mo	-0.04 (0.38)	-0.07 (0.42)	0.029
WBC slope t_{-12} to t_0, $*10^9$/l/mo	0.02 (0.33)	0.01 (0.25)	0.245
eGFR slope t_{-12} to t_0, ml/min/1.73m^2/mo	-0.64 (0.77)	-0.45 (0.54)	<0.001
SBP slope t_{-12} to t_0, mmHg/mo	0.13 (2.76)	-0.04 (2.54)	0.075
Weight slope t_{-12} to t_0, kg/mo	-0.15 (1.12)	-0.11 (1.27)	0.424
Albumin t_0, g/dl	3.6 (0.48)	3.64 (0.44)	0.008
Corrected calcium t_0, mg/dl	8.83 (0.8)	8.95 (0.73)	<0.001
Hemoglobin t_0, g/dl	10 (1.32)	10.6 (1.39)	<0.001
Phosphorus t_0, mg/dl	5.28 (1.31)	5.28 (1.18)	0.973
Sodium t_0, mmol/l	139.36 (3.15)	139.24 (2.98)	0.250
WBC t_0, $*10^9$/l	7.55 (3.28)	7.48 (2.4)	0.474
eGFR t_0, ml/min/1.73m^2	9.85 (4.13)	7.84 (3.21)	<0.001
SBP t_0, mmHg	144.53 (19.94)	141.08 (19.01)	<0.001
Weight t_0, kg	89.96 (25.5)	88.24 (22.79)	0.059
Albumin slope t_0 to t_{+12}, g/dl/mo	0.01 (0.04)	0 (0.04)	<0.001
Corrected calcium slope t_0 to t_{+12}, mg/dl/mo	0.01 (0.07)	0 (0.08)	0.056
Hemoglobin slope t_0 to t_{+12}, g/dl/mo	0.04 (0.13)	-0.01 (0.15)	<0.001
Phosphorus slope t_0 to t_{+12}, mg/dl/mo	0.02 (0.15)	0.02 (0.15)	0.663
Sodium slope t_0 to t_{+12}, mmol/l/mo	-0.02 (0.31)	-0.08 (0.34)	<0.001
WBC slope t_0 to t_{+12}, $*10^9$/l/mo	-0.03 (0.24)	0.01 (0.25)	<0.001
SBP slope t_0 to t_{+12}, mmHg/mo	-0.08 (3.83)	-0.21 (2.88)	0.393
Weight slope t_0 to t_{+12}, kg/mo	0.09 (2.27)	0.18 (3.5)	0.614
Albumin t_{+12}, g/dl	3.81 (0.35)	3.54 (0.42)	<0.001
Corrected calcium t_{+12}, mg/dl	9.06 (0.57)	8.95 (0.66)	<0.001
Hemoglobin t_{+12}, g/dl	10.84 (0.92)	10.91 (1.28)	0.117
Phosphorus t_{+12}, mg/dl	5.26 (1.22)	5.33 (1.33)	0.135
Sodium t_{+12}, mmol/l	138.24 (2.88)	138.29 (3.25)	0.660
WBC t_{+12}, $*10^9$/l	7.06 (2.51)	7.68 (2.67)	<0.001
SBP t_{+12}, mmHg	136.65 (20.96)	136.54 (19.89)	0.905
Weight t_{+12}, kg	84.58 (24.1)	87.73 (23.56)	0.008

All continuous variables are shown as mean (standard deviation).

Table 5.2 Demographics and pre-dialysis trajectories as intention-to-treat, matched for age and diabetes.

	Starting HD	Starting PD	p-value (between 2 groups)
Number of patients	1006	1006	
Black race, %	29%	24%	0.006
Male, %	55%	56%	0.654
Diabetes mellitus, %	47%	47%	1.000
Married, %	36%	43%	0.001
Age, years	59.06 (14.04)	59.06 (14.04)	1.000
Albumin t_{-12}, g/dl	3.71 (0.46)	3.69 (0.45)	0.429
Corrected calcium t_{-12}, mg/dl	8.99 (0.72)	8.97 (0.67)	0.565
Hemoglobin t_{-12}, g/dl	10.67 (1.48)	10.82 (1.45)	0.047
Phosphorus t_{-12}, mg/dl	4.79 (1.14)	4.85 (1.04)	0.322
Sodium t_{-12}, mmol/l	139.59 (3)	139.71 (3.04)	0.451
WBC t_{-12}, $*10^9$/l	7.57 (2.66)	7.46 (2.16)	0.414
eGFR t_{-12}, ml/min/1.73m^2	14.98 (8.08)	11.62 (6.1)	<0.001
SBP t_{-12}, mmHg	143.57 (19.35)	141.61 (18.32)	0.037
Weight t_{-12}, kg	92.27 (26.88)	89.74 (23.41)	0.046
Albumin slope t_{-12} to t_0, g/dl/mo	-0.01 (0.05)	-0.01 (0.06)	0.968
Corrected calcium slope t_{-12} to t_0, mg/dl/mo	-0.01 (0.09)	0 (0.09)	0.030
Hemoglobin slope t_{-12} to t_0, g/dl/mo	-0.08 (0.18)	-0.01 (0.21)	<0.001
Phosphorus slope t_{-12} to t_0, mg/dl/mo	0.08 (0.18)	0.05 (0.17)	0.001
Sodium slope t_{-12} to t_0, mmol/l/mo	-0.03 (0.37)	-0.07 (0.42)	0.030
WBC slope t_{-12} to t_0, $*10^9$/l/mo	0.01 (0.49)	0.01 (0.25)	0.922
eGFR slope t_{-12} to t_0, ml/min/1.73m^2/mo	-0.59 (1.05)	-0.45 (0.54)	0.001
SBP slope t_{-12} to t_0, mmHg/mo	0.1 (2.67)	-0.03 (2.55)	0.296
Weight slope t_{-12} to t_0, kg/mo	-0.2 (1.2)	-0.11 (1.28)	0.157
Albumin t_0, g/dl	3.63 (0.48)	3.64 (0.44)	0.733
Corrected calcium t_0, mg/dl	8.85 (0.86)	8.95 (0.73)	0.005
Hemoglobin t_0, g/dl	10.02 (1.33)	10.61 (1.39)	<0.001
Phosphorus t_0, mg/dl	5.4 (1.35)	5.28 (1.18)	0.042
Sodium t_0, mmol/l	139.2 (3.13)	139.24 (2.97)	0.789
WBC t_0, $*10^9$/l	7.57 (3.2)	7.5 (2.39)	0.608
eGFR t_0, ml/min/1.73m^2	9.25 (3.89)	7.84 (3.21)	<0.001
SBP t_0, mmHg	144.84 (20.77)	141.16 (19.03)	<0.001
Weight t_0, kg	91.17 (26.46)	88.42 (22.8)	0.034
Albumin slope t_0 to t_{+12}, g/dl/mo	0.01 (0.04)	0 (0.04)	<0.001
Corrected calcium slope t_0 to t_{+12}, mg/dl/mo	0 (0.07)	0 (0.08)	0.536
Hemoglobin slope t_0 to t_{+12}, g/dl/mo	0.04 (0.15)	-0.01 (0.15)	<0.001
Phosphorus slope t_0 to t_{+12}, mg/dl/mo	0.01 (0.17)	0.02 (0.15)	0.088
Sodium slope t_0 to t_{+12}, mmol/l/mo	-0.03 (0.32)	-0.08 (0.34)	<0.001
WBC slope t_0 to t_{+12}, $*10^9$/L/mo	-0.03 (0.29)	0.01 (0.25)	0.004
SBP slope t_0 to t_{+12}, mmHg/mo	-0.07 (3.33)	-0.2 (2.87)	0.557
Weight slope t_0 to t_{+12}, kg/mo	0.22 (2.04)	0.18 (3.51)	0.809
Albumin t_{+12}, g/dl	3.85 (0.35)	3.54 (0.42)	<0.001
Corrected calcium t_{+12}, mg/dl	9.06 (0.62)	8.95 (0.66)	<0.001
Hemoglobin t_{+12}, g/dl	10.83 (0.95)	10.91 (1.28)	0.112
Phosphorus t_{+12}, mg/dl	5.38 (1.29)	5.33 (1.32)	0.417
Sodium t_{+12}, mmol/l	138.31 (2.79)	138.29 (3.24)	0.883
WBC t_{+12}, $*10^9$/l	7.21 (3.15)	7.69 (2.67)	<0.001
SBP t_{+12}, mmHg	138.28 (21.08)	136.64 (19.9)	0.259
Weight t_{+12}, kg	88.4 (27.02)	87.87 (23.52)	0.784

All continuous variables are shown as mean (standard deviation).

Pre- and post-dialytic trajectories

When visually comparing pre-dialytic trajectories in intention-to-treat patients (Figures 5.2A-I), from 1 month before to 1 month after dialysis start, a sharp decline in SBP was observed in HD starters compared to more gradual changes in PD starters. Also, a more pronounced decline in Wt was observed in HD compared to PD starters during the early transition period followed by a stabilization whereas a gradual increase in Wt was observed after the start of PD. In addition, a sharp temporary drop in Phos was observed in the early transition period in HD starters, followed by a rise in the later transition period compared to more gradual changes in PD starters. Regarding serum sodium, a sharp decline was observed in the HD starters from 2 months before dialysis start to 1 month after dialysis start, with relative stabilization afterwards, in contrast to the more gradual decline in serum sodium after the start of dialysis in PD starters. WBC counts declined after the start of dialysis in HD starters in contrast to a relatively stable trend in PD starters. A pronounced post-dialytic difference between HD and PD starters was observed for Alb, showing a pronounced increase in HD as compared to PD starters. The visual representation confirmed the sharper decline in eGFR before the start of dialysis and the pronounced pre-dialytic drop and post-dialytic rise in Hgb in HD starters.

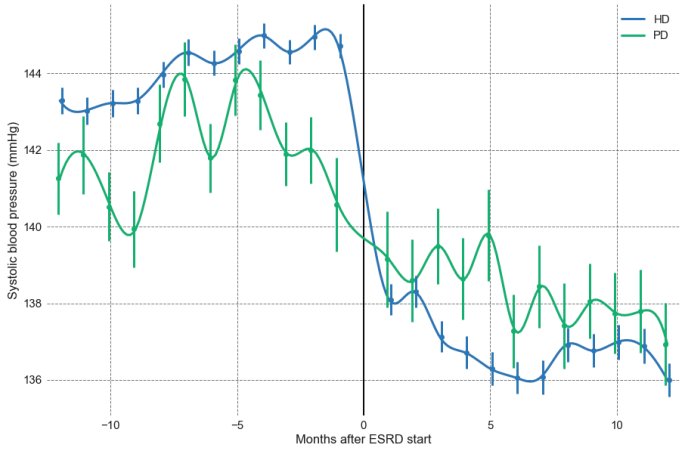

Figure 5.2A Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **systolic blood pressure** (mmHg).

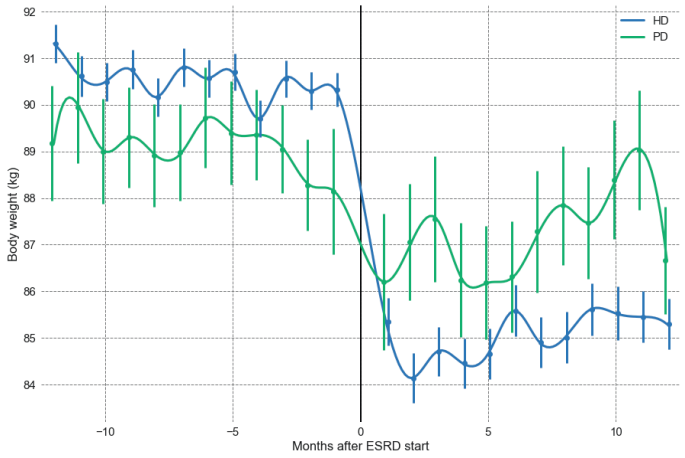

Figure 5.2B Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **weight** (kg).

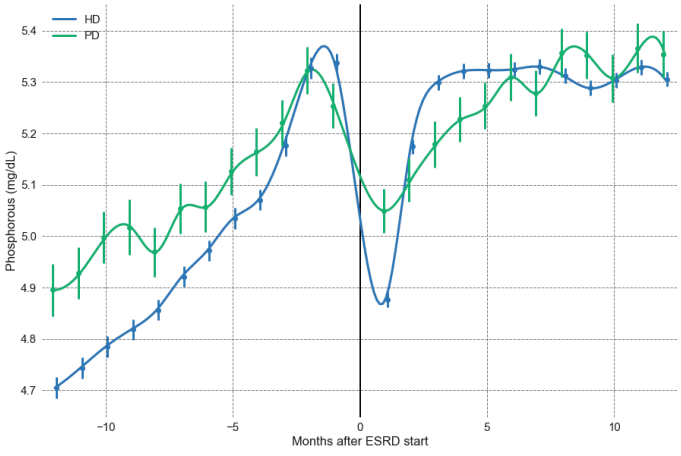

Figure 5.2C Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **phosphorus** (ml/dl).

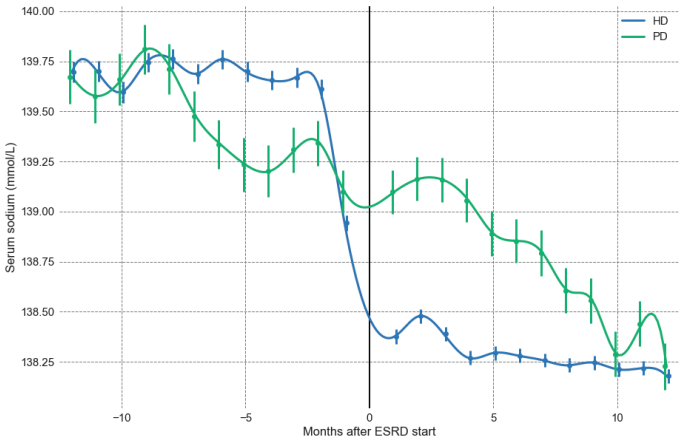

Figure 5.2D Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **sodium** (mmol/l).

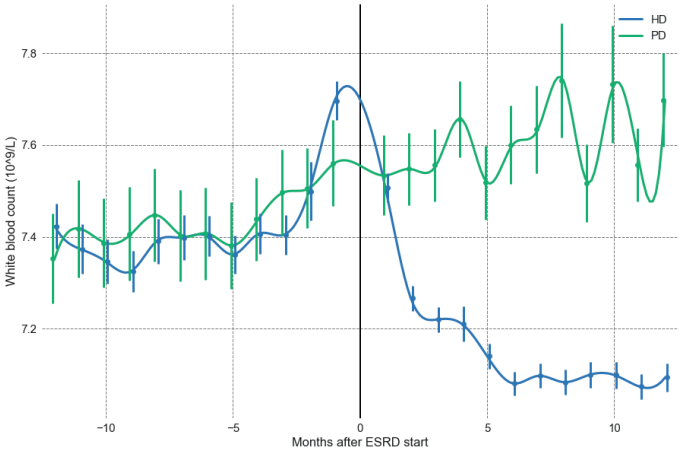

Figure 5.2E Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **white blood cell count** (*10^9/l).

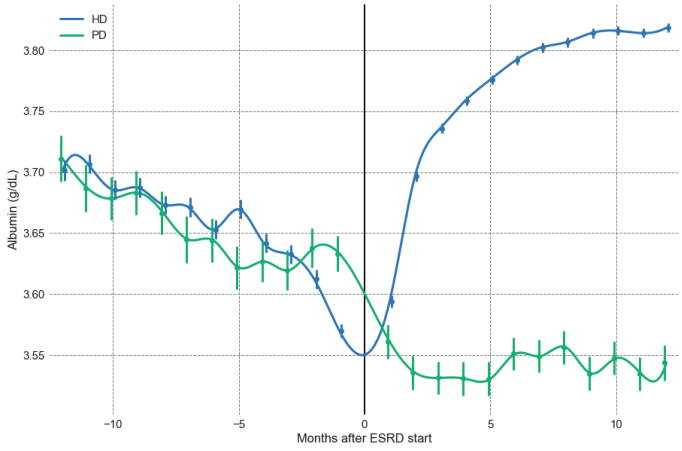

Figure 5.2F Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **albumin** (g/dl).

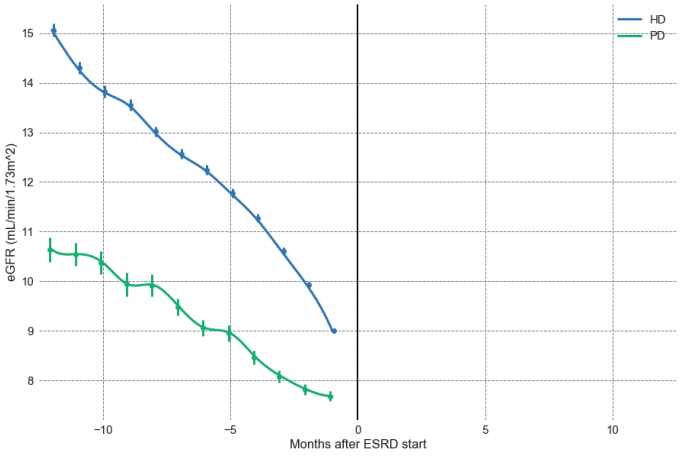

Figure 5.2G Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **eGFR** (ml/min/1,73m^2).

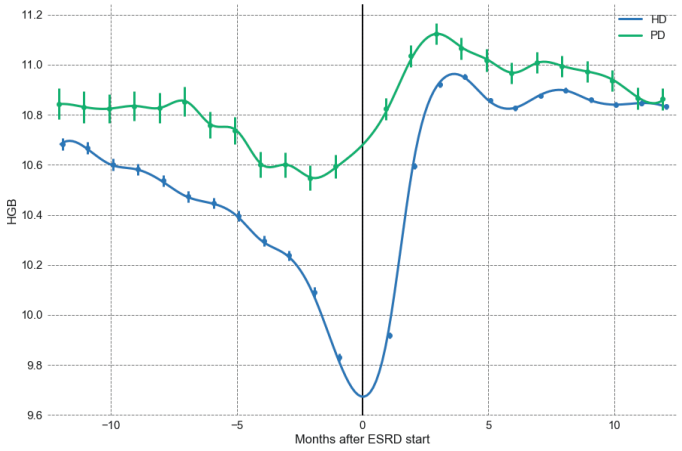

Figure 5.2G Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **hemoglobin** (g/dl).

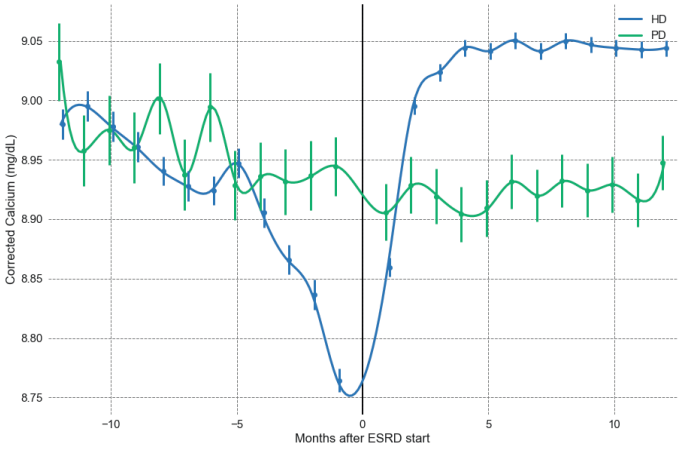

Figure 5.2H Graph displaying the change in parameters during monthly intervals (intention-to-treat patients), **corrected calcium** (mg/dl).

Discussion

This study aimed to investigate trajectories of clinical and laboratory parameters in cardiovascular, nutritional, inflammatory, and mineral metabolism domains in patients starting PD and HD through the transition period. The transition period described in this

paper includes the 12 months before and 12 months after dialysis start in patients receiving pre-dialytic nephrology care. Studies describing the transition period are rare since patient data are usually not included in a single database. We believe our study is unique in the respect that both pre- and post-dialytic clinical parameter trajectories could be followed in individual patients during a critical transition period, which is generally associated with an elevated mortality risk.[11-13]

The first part of this study focused on differences in pre-dialytic trajectories between HD and PD starters. In accordance with previous studies, HD starters were generally older compared to PD starters. In our study, PD starters were less likely to be diabetic, which agrees with some, but not all studies.[2-4,14] Also, in this study HD and PD starters were equally likely to be black (25% vs. 24%). Other studies have reported incident HD starters to be more likely to be black compared to PD starters, (31% vs. 20%) in a large U.S. dataset.[4]

At 12 months before dialysis start, no major differences in the study parameters were observed between the 2 groups although a slightly higher SBP and lower Phos were observed in PD patients. The differences in SBP and Phos at this time point between the groups lost significance when the groups were matched for age and DM.

Pre-dialytic slopes of SBP and Alb, which we earlier identified as being significantly different between patients who survived or did not survive the year after dialysis start,[9] were not different between PD and HD starters. However, a decline in Alb before dialysis start in both PD and HD starters in the intention-to-treat analysis, possibly reflects malnutrition, fluid overload, or both in the pre-dialysis period.

Differences were observed in eGFR levels which were significantly lower in PD starters 12 months before dialysis start, as well as at the time of dialysis start. When comparing eGFR slopes during the 12 months before dialysis start, HD starters experienced a more rapid decline in eGFR compared to PD starters, but started dialysis at a higher eGFR level. Concomitantly, the rise in Phos and decline in Hgb levels were more pronounced in HD starters, possibly related to the sharper decline in renal function. The faster decline in eGFR between HD and PD starters may be relevant, given the fact that steeper eGFR slopes in the pre-dialytic period have been related to increased mortality.[7,8] It should also be noted that the steeper eGFR slope may only reflect the higher initial eGFR for HD starters. Also, a more rapid than expected eGFR decline may predispose patients to an HD start. Ideally, future studies comparing outcomes between PD and HD in incident patients should match for pre-dialytic eGFR trajectories. It is of note that Mehrotra et al, in a study of U.S. incident patients who survived 90 days on dialysis, showed that average eGFR at dialysis start was the same for HD and PD starters (8.9 ml/min/1.73m^2).[4] The reason HD starters initiated dialysis at a higher eGFR compared to PD starters in our study is unknown, but differences in the clinical decision process for these nephrology practice patients, triggered by the more rapid decline in eGFR in HD starters, might have played a role.[8]

The second part of this study focused on clinical parameter trajectories after dialysis start. Previous studies demonstrate that Alb increases during the 12 months after dialysis start,[9,11,15] possibly due to an improvement in nutritional state or a reduction of fluid overload state.[11,15-17] In the present study, PD starters did not experience an increase in Alb levels compared to HD starters, which held true both for an intention-to-treat analysis and in the as-treated analysis comparing patients who remained on their initial treatment for the entire 12 months. This finding may be relevant, as Alb trajectories were found to be related to both mortality and technique failure in PD patients.[17,18] However, it is well known that Alb levels are lower in prevalent PD as compared to HD patients.[14] A higher protein loss during PD may be implicated in these differences, which may have less of an effect on the risk prediction potential of Alb levels when compared to the effects of inflammation and/or malnutrition. Indeed, Mehrotra et al have shown that whereas Alb was predictive of outcome in both HD and PD patients, equal mortality rates between both groups were observed at lower levels of Alb in the latter group.[14]

For the inflammatory dimension, only WBC counts were available. We acknowledge that this is a relatively crude index of inflammation, although WBC counts have been found to be related to outcome in dialysis patients.[19] In a previous study,[9] we observed different WBC slopes between patients who survived or did not survive the first year on dialysis. Interestingly, slopes of the WBC count after dialysis start were significantly different between PD and HD starters, with PD starters exhibiting higher values 12 months after dialysis start. Although, when comparing curves in detail, the difference appeared predominantly related to a WBC decline in HD starters instead of an increase in PD starters. The clinical relevance of these findings is uncertain, as differences between both groups were subtle. If confirmed in future studies, possible explanations include the pro-inflammatory effect of PD catheter insertion or PD fluid bio-incompatibility.[20-24] Due to the design of the database, we do not have data on treatment characteristics of PD patients, nor on central venous catheter (CVC) use of the HD patients included in our study, but from previous studies of our group[25] in patients receiving pre-dialytic care we can estimate that around 65% of the nephrology practice HD population initiated treatment with a CVC.

In PD starters, a larger decline in serum sodium levels was observed compared to HD starters, although after 12 months, sodium levels were not significantly different between PD and HD starters. Of note, low serum sodium levels are predictive of mortality in dialysis patients.[26,27] Sodium appears to be a composite parameter which, in addition to hydration, is also influenced by malnutrition and inflammation in ESRD patients.[27,28] However, the decline in serum sodium levels in PD may also be due to direct effect of the treatment itself.[29] It would be informative to see whether, in analogy to serum Alb levels,[14] serum sodium levels have a differential outcome effect in PD as compared to HD patients.[29]

Lastly, in both intention-to-treat as well as in as-treated patients, Wt was significantly higher in PD starters at 12 months after dialysis start, whereas it was higher in HD starters 12 months before dialysis start. This is consistent with slopes in Wt changes after dialysis start which tended to be higher in PD starters. Notably, HD starters experienced a rapid decline in Wt at the time of dialysis start in contrast to PD starters. Since Wt is a composite parameter, which is influenced by fluid changes, as well as by changes in lean tissue mass and fat mass[30] it is difficult to interpret these results in the absence of exact measurements of body composition. However, in general, an increase in Wt in the weeks and months following dialysis start is associated with improved survival.[31,32]

Slopes for variables in the other domains following dialysis start were, in general, not significantly different between the groups, suggesting indirectly that potential differences in fluid overload in PD compared to HD starters are not yet apparent in the year following dialysis start.[33] However, shortly after dialysis start, a sharp decline in SBP was observed in HD starters in contrast to the more gradual change in PD starters, possibly due to the brisker correction of fluid overload in the former group.

In our study, a relatively low percentage of patients started with PD, in agreement with previous studies in a U.S. population. This shows that even with prolonged pre-dialysis care, the relative contribution of PD in the treatment spectrum of incident dialysis patients is low. Special attention to treatment preparation and patient choice process, for instance by a renal care coordinator as discussed in our previous paper, could increase the penetration of PD as an initial therapy.[25]

Our descriptive dataset sheds new light on both pre- and post-dialysis initiation trajectories in PD and HD starters due to the unique design of the database. We believe our data are robust as they were observed in an intention-to-treat analysis as well as in an as-treated analysis, and persisted after matching. However, due to the strict de-identification policy of the database, important patient and treatment characteristics are missing and the number of study variables is limited. In addition, despite matching for age, sex, and diabetes mellitus there are other significant potential confounders that are unaccounted for that may influence modality choice and outcome. Therefore, our study should be regarded as hypothesis generating and the results should be confirmed in future studies. In addition, whereas we analyzed slopes obtained by regression analysis, we should acknowledge that certain trajectories do not follow a linear pattern. The addition of graphical data hopefully allows comparison of parameters at different time points. However, we should point out that aggregated means are reported during each month since data are not always available for all patients monthly.

Conclusion

Patients starting PD or HD have no major differences in relevant clinical and laboratory parameters reflecting cardiovascular, nutritional, inflammatory, and mineral metabolism domains 12 months before dialysis start and no major differences in pre-dialytic slopes. However, HD starters experienced a more rapid decline in eGFR before the start of dialysis. Ideally, eGFR trajectories in the pre-dialytic period should be considered when comparing early outcomes between PD and HD starters. Following dialysis start, subtle differences in slopes of serum sodium, Alb and WBC count were observed between HD and PD starters, of which the prognostic significance remains to be studied.

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Supplementary Table S5.1 Trajectories of PD and HD patients who remain on starting modality as-treated.

	Always HD	Always PD	p-value (between 2 groups)
Number of patients	7760	825	
Black race, %	26%	24%	0.196
Male, %	56%	56%	0.891
Diabetes mellitus, %	59%	46%	<0.001
Married, %	39%	44%	0.006
Age, years	64.31 (12.84)	59.03 (14.03)	<0.001
Albumin t_{-12}, g/dl	3.69 (0.46)	3.71 (0.44)	0.156
Corrected calcium t_{-12}, mg/dl	8.99 (0.67)	8.99 (0.66)	0.892
Hemoglobin t_{-12}, g/dl	10.71 (1.45)	10.82 (1.43)	0.056
Phosphorus t_{-12}, mg/dl	4.63 (1.02)	4.78 (1.01)	<0.001
Sodium t_{-12}, mmol/l	139.79 (3.03)	139.7 (3.05)	0.452
WBC t_{-12}, $*10^9$/l	7.4 (2.75)	7.49 (2.16)	0.371
eGFR t_{-12}, ml/min/1.73m^2	15.54 (7.68)	11.74 (5.94)	<0.001
SBP t_{-12}, mmHg	143.36 (19.81)	141.31 (18.37)	0.007
Weight t_{-12}, kg	91 (24.94)	88.67 (22.39)	0.014
Albumin slope t_{-12} to t_0, g/dl/mo	-0.01 (0.05)	-0.01 (0.06)	0.341
Corrected calcium slope t_{-12} to t_0, mg/dl/mo	-0.02 (0.09)	0 (0.09)	<0.001
Hemoglobin slope t_{-12} to t_0, g/dl/mo	-0.08 (0.18)	-0.01 (0.21)	<0.001
Phosphorus slope t_{-12} to t_0, mg/dl/mo	0.08 (0.17)	0.05 (0.15)	<0.001
Sodium slope t_{-12} to t_0, mmol/l/mo	-0.04 (0.39)	-0.07 (0.45)	0.062
WBC slope t_{-12} to t_0, $*10^9$/l/mo	0.02 (0.34)	0.01 (0.2)	0.328
eGFR slope t_{-12} to t_0, ml/min/1.73m^2/mo	-0.63 (0.77)	-0.44 (0.51)	<0.001
SBP slope t_{-12} to t_0, mmHg/mo	0.13 (2.77)	-0.06 (2.56)	0.073
Weight slope t_{-12} to t_0, kg/mo	-0.15 (1.12)	-0.11 (1.16)	0.439
Albumin t_0, g/dl	3.6 (0.48)	3.66 (0.43)	<0.001
Corrected calcium t_0, mg/dl	8.83 (0.8)	8.97 (0.72)	<0.001
Hemoglobin t_0, g/dl	9.99 (1.31)	10.62 (1.37)	<0.001
Phosphorus t_0, mg/dl	5.27 (1.31)	5.24 (1.15)	0.440
Sodium t_0, mmol/l	139.36 (3.15)	139.25 (3.04)	0.341
WBC t_0, $*10^9$/l	7.55 (3.3)	7.49 (2.2)	0.480
eGFR t_0, ml/min/1.73m^2	9.86 (4.15)	7.94 (3.17)	<0.001
SBP t_0, mmHg	144.47 (19.97)	140.84 (18.55)	<0.001
Weight t_0, kg	89.94 (25.61)	86.9 (21.71)	0.002
Albumin slope t_0 to t_{+12}, g/dl/mo	0.02 (0.04)	0 (0.04)	<0.001
Corrected calcium slope t_0 to t_{+12}, mg/dl/mo	0.01 (0.07)	0 (0.08)	0.002
Hemoglobin slope t_0 to t_{+12}, g/dl/mo	0.04 (0.13)	-0.01 (0.14)	<0.001
Phosphorus slope t_0 to t_{+12}, mg/dl/mo	0.02 (0.15)	0.03 (0.12)	0.055
Sodium slope t_0 to t_{+12}, mmol/l/mo	-0.02 (0.31)	-0.08 (0.32)	<0.001
WBC slope t_0 to t_{+12}, $*10^9$/l/mo	-0.03 (0.23)	0.02 (0.24)	<0.001
SBP slope t_0 to t_{+12}, mmHg/mo	-0.07 (3.82)	-0.31 (2.53)	0.102
Weight slope t_0 to t_{+12}, kg/mo	0.08 (2.28)	0.3 (3.47)	0.226
Albumin t_{+12}, g/dl	3.82 (0.34)	3.52 (0.42)	<0.001
Corrected calcium t_{+12}, mg/dl	9.06 (0.57)	8.94 (0.67)	<0.001
Hemoglobin t_{+12}, g/dl	10.84 (0.9)	10.98 (1.3)	0.003
Phosphorus t_{+12}, mg/dl	5.26 (1.22)	5.28 (1.31)	0.577
Sodium t_{+12}, mmol/l	138.22 (2.86)	138.36 (3.36)	0.251
WBC t_{+12}, $*10^9$/l	7.04 (2.5)	7.79 (2.76)	<0.001
SBP t_{+12}, mmHg	136.64 (21.06)	136.24 (19.61)	0.694
Weight t_{+12}, kg	84.56 (24.25)	87.19 (22.78)	0.032

All continuous variables are shown as mean (standard deviation).

Supplementary Table S5.2 Mean, standard deviation, and percentiles for number of data entries for each patient for each variable, prior to and after dialysis start.

	Mean (stdev) 12 months before dialysis start	Mean (stdev) 12 months after dialysis start
Albumin (g/dl)	6.2 (4)	11.8 (2.6)
Hgb (g/dl)	9.2 (9.7)	37.8 (14.8)
Phosphorus (mg/dl)	6.4 (4.7)	13.3 (4.3)
Sodium (mmol/l)	7.4 (4.6)	11.2 (2.9)
WBC (10^9/l)	6 (4.3)	11.4 (2.9)
eGFR (ml/min/1.73m^2)	4.3 (4.1)	2.1 (2.7)
SBP (mmHg)	2.9 (3)	4.7 (5)
Weight (kg)	2.7 (2.7)	3.6 (3.9)
Corrected calcium (mg/dl)	6.1 (4)	11.1 (2.7)

Chapter 6

Longitudinal patterns of health-related quality of life and dialysis modality: a national cohort study

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Submitted

Abstract

Background

Health-related quality of life (HrQoL) varies among dialysis patients. However, little is known about the association of dialysis modality with HrQoL over time. We describe longitudinal patterns of HrQoL among chronic dialysis patients by treatment modality.

Methods

National retrospective cohort study of adult patients who initiated in-center dialysis or a home modality (peritoneal or home hemodialysis) between 1/2013 and 6/2015. Patients remained on the same modality for the first 120 days of the first two years and survived at least 485 days. HrQoL was assessed by the Kidney Disease and Quality of Life-36 (KDQOL) survey in the first 120 days of the first two years after dialysis initiation. Home modality patients were matched to in-center patients in a 1:5 fashion.

Results

In-center (n=4234) and home modality (n=880) patients had similar demographic and clinical characteristics. In-center dialysis patients had lower mean KDQOL scores across several domains compared to home modality patients. For patients who remained on the same modality, there was no change in HrQoL. However, there were clinically meaningful changes in certain aspects of HrQoL for patients who switched modalities. Specifically, physical functioning decreased for patients who switched from home to in-center dialysis ($p < 0.05$).

Conclusions

Among a national cohort of chronic dialysis patients, different patterns of HrQoL life were observed only among patients who changed modalities. Patients who switched from home to in-center modalities had significant lower physical functioning over time. Providers and patients should be mindful of HRQoL changes that may occur after dialysis modality change.

Introduction

Approximately 680,000 patients in the United States are afflicted with end-stage renal disease (ESRD) and roughly 70% of these patients receive maintenance therapies in the form of hemodialysis (HD) or peritoneal dialysis (PD).[1] Compared to the general population, dialysis patients have lower health-related quality of life (HRQoL), which is strongly associated with poorer dialysis adherence, increased hospitalizations, and higher mortality.[2-5] Importantly, although in-center HD patients and home modality patients appear to have different patterns of HRQoL, it is unclear if one modality type results in improved health status.[5-10] For instance, one study explored quality of life among 16,755 in-center HD patients and 1,260 PD patients and found no significant difference in the physical aspects of the SF-36 survey between the two groups, although PD patients scored higher on mental aspects.[8] Notably, this study focused on cross-sectional relationships between HRQoL and dialysis modality.

Several studies have compared HRQoL changes over time between incident ESRD patients receiving different renal replacement therapy modalities (e.g., in-center HD, home dialysis, and renal transplantation), however most have featured small sample sizes, shorter follow-up times, or have primarily focused on stable modality choices over time.[11-18] To our knowledge, there have not been any studies that have examined changes in HRQoL over time based on modality change among a large national cohort of chronic dialysis patients. Specifically, we investigated whether changes in HRQoL over time would be different for patients who remained on the same modality versus patients who changed modality.

Materials and methods

Study population and data source

Approximately 43% of the current United States outpatient dialysis population is represented in the Fresenius Medical Care North America (FMCNA) database.[19] We utilized data from patients ≥18 years of age who received any dialysis treatment within the FMCNA network of outpatient clinics between January 1, 2013 and June 30, 2015. We included patients who had their first outpatient dialysis treatment with FMCNA within 120 days of dialysis initiation and who survived at least 485 days. Patients were only included if they remained on the same treatment modality for the first 120 days of the first year and second year. Patients were categorized as using a home dialysis modality (e.g., PD [n=825] and home hemodialysis (HHD) [n=61]) or receiving in-center HD treatments (n=19,129) based on their first modality recorded in the FMCNA database. We also relied on the FMCNA database to ascertain changes in dialysis modality 1) within the first 120 days of dialysis initiation (Period 1); and 2) between 365

and 485 days after dialysis initiation (Period 2). Next, we performed chart reviews of 40 randomly selected patients to assess the accuracy of recorded dialysis modality data. Baseline data on patient demographics, number of comorbidities, catheter use (central venous and peritoneal), residual renal function, blood pressure, and laboratory variables were ascertained within the first 120 days of dialysis initiation using the FMCNA database. We confirmed presence of residual renal function and catheter use if these were documented on the first day of dialysis initiation. For patients who had multiple lab values within the first 120 days, mean levels were calculated and used for analysis.

Outcomes

We used the Kidney Disease and Quality of Life (KDQOL-36) survey to assess HRQoL for all patients who had completed at least two surveys within the study period.[20] This instrument has been used extensively to assess HRQoL among incident and prevalent dialysis patient populations and includes the Physical Component Summary (PCS), Mental Component Summary (MCS), Symptom/Problems (SPS), Burden of Kidney Disease (BKD), and Effects of Kidney Disease (EKD) subscales. To ascertain changes in HRQoL over time, we reviewed KDQOL data during Period 1 and Period 2. All KDQOL surveys are maintained in FMCNA dialysis facilities and are accurate for all patients based on mandatory rules.

Statistical analysis

Patient characteristics were described using percentages for categorical variables and mean $\pm$ standard deviation (SD) for continuous variables. To control for any confounding effects, we randomly selected patients using a home modality and receiving in-center dialysis and matched them by sex, age, race, albumin, number of comorbidities, and presence of residual renal function. We assessed change in each KDQOL subscale score between Period 1 and 2 and reported the change as a percentage. Two-sided p values less than 0.05 were used to indicate statistical significance. All analyses were conducted using SAS software (version 9.3; SAS Institute Inc., Cary, NC) and matching was performed using the MatchIt package in R.[21]

A protocol detailing this retrospective analysis was reviewed by Schulman Institutional Review Board (IRB) in Cincinnati, OH and determined to be exempt from regulatory approval in accordance with the Common Rule, Title 45 Code of Federal Regulations (CFR) Part 46. This study did not require informed consent and was performed in adherence with the Declaration of Helsinki.

Results

Patient characteristics

During the study period, we identified a total of 880 patients who initiated treatment with a home modality at a chronic dialysis facility affiliated with FMCNA and met eligibility criteria. Home modality patients were matched in a 1:5 fashion to 4234 in-center patients (Figure 6.1). Matching procedures resulted in relatively similar distributions of demographic and clinical variables between the two groups (Table 6.1). The mean ages ± SD for in-center patients and home modality patients were 60.9±14 and 57.3±14.5 years, respectively ($p<0.01$). Compared to home modality patients, there was a higher proportion of in-center dialysis patients who were of Hispanic ethnicity (11% vs. 8%, $p<0.01$), but no differences in terms of sex or race. In-center HD patients also had less commonly attained a bachelor's level of education (54% vs. 56%, $p<0.01$) compared to home modality patients, however there was no significant difference in marital status or mean annual household income between the two groups.

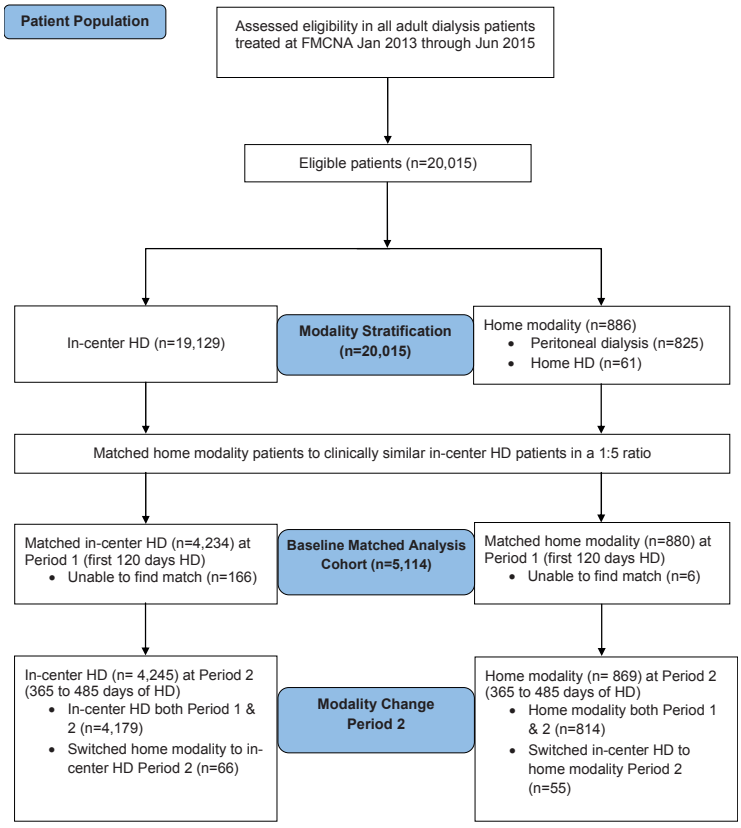

Figure 6.1 Flow chart.

Table 6.1 Baseline patient characteristics,*

Variables	All (n=5114)	In-center (n=4234)	Home (n=880)	p-value
Mean age (years)	60.3 (14.1)	60.9 (14)	57.3 (15)	<0.01
Male	56	56	54	0.25
Hispanic ethnicity	11	11	8	<0.01
Black race	23	22	25	0.07
Mean annual household income (dollars/year)	50888 (19073)	50901 (19098)	50828 (18960)	0.92
Education (bachelors and higher)	54	54	56	<0.01
Married	42	42	45	0.10
Number of comorbidities	16 (9)	17 (9)	15 (10)	<0.01
Catheter access use	60	53	95	<0.01
Presence of any residual renal function	89	88	89	0.71
Mean serum sodium (mmol/l)	138.8 (2.8)	138.5 (2.7)	139.9 (2.9)	<0.01
Mean albumin (g/dl)	3.7 (0.4)	3.7 (0.4)	3.7 (0.4)	0.33
Mean hemoglobin (g/dl)	10.7 (0.9)	10.7 (0.8)	11 (1.2)	<0.01
Mean systolic blood pressure (mmHg)	142.4 (15.9)	142.5 (15.6)	141.3 (22)	0.48
Mean body mass index (kg/m^2)	30.4 (9.1)	30.4 (9.2)	30 (6.3)	0.34
Mean physical composite summary score (PCS)	38.6 (10.4)	38 (10.3)	41.1 (10.5)	<0.01
Mean mental composite summary score (MCS)	51.7 (10)	51.8 (10)	51.4 (9.7)	0.27
Mean symptom problem score (SPS)	81 (14.1)	80.7 (14.3)	82.7 (13.4)	<0.01
Mean burden of kidney disease score (BKD)	54 (28)	53.2 (28)	58 (27.6)	<0.01
Mean effects of kidney disease score (EKD)	77.2 (19.8)	76.6 (20.1)	79.7 (17.7)	<0.01

*Categorical variables are presented as percentages; continuous variables are presented as mean (± standard deviation).

In-center dialysis patients had a higher mean number of comorbidities versus home modality patients (17±9 vs. 15±10, p<0.01). Furthermore, 53% of in-center dialysis patients used catheters compared to 95% of home modality patients (p<0.01). Compared to home modality patients, in-center dialysis patients also had lower mean serum sodium (138.5±2.7 vs. 139.9±2.9, p<0.01) and hemoglobin levels (10.7±0.8 vs. 11±1.2, p<0.01). There were no differences in residual renal function, mean albumin, mean systolic blood pressure and mean body mass index between the two groups (Table 6.1).

In terms of baseline HRQOL, in-center patients had lower mean KDQOL scores compared to home modality patients for almost all subscales. For the PCS subscale, in-center dialysis patients scored 38±10.3 (p<0.01) whereas home modality patients scored 41.1±10.5 (p<0.01). Similarly, scores were lower on the SPS (80.7±14.3 vs. 82.7±13.4, p<0.01) and EKD subscales (76.6±20.1 vs. 79.7±17.7, p<0.01) for in-center versus home modality patients. The largest difference in mean scores between the two groups occurred on the BKD subscale (53.2±28 for in-center vs. 58±27.6 for home modality patients, p<0.01). There was no difference in MCS subscale scores between the two groups (Table 6.1).

Changes in HRQOL over time

Out of 40 charts reviewed, 100% of patients who stayed on the same dialysis modality accurately matched the modality listed in the FMCNA database. Additionally, 100% of patients who switched modalities matched the modalities listed in the FMCNA database. Changes in mean KDQOL scores between Period 1 and Period 2 based on dialysis modality are displayed in Table 6.2. Out of 5114 patients, 4179 remained on in-center dialysis and 814 remained on home modalities. For patients who changed dialysis modalities, 55 switched from in-center to a home modality and 66 switched from a home modality to in-center dialysis.

Overall, the magnitude of change in KDQOL subscale scores overtime ranged between 0.4% to 1.0% depending on dialysis modality. Using established criteria for minimal clinically meaningful change (3 to 5 units),[22,23] HRQOL did not change over time for patients who remained on in-center dialysis or home modalities. However, patients who switched from in-center dialysis to home modalities had a large increase in the BKD (14.1%) and EKD subscale scores (7.8%). In comparison, patients who switched from a home modality to in-center dialysis had relatively large decreases in the PCS (-8.9%) and BKD (-6.3%) subscale scores over time ($p<0.05$). Apart from a decrease in PCS scores for patients who switched from a home modality to in-center dialysis, changes in KDQOL subscale scores over time were not statistically significant (Table 6.2).

Discussion

Among a national cohort of adult patients who initiated chronic in-center or home dialysis, HRQoL varied by dialysis modality. In-center dialysis patients had lower mean KDQOL subscale scores compared to home modality patients at baseline. For patients who remained on the same modality, there was no significant change in HRQoL over time. However, patients who switched modalities had clinically meaningful changes in certain KDQOL subscale scores. Specifically, home modality patients who switched to in-center dialysis had significantly lower physical functioning over time.

Monitoring and promoting the well-being of dialysis patients along the spectrum of their kidney disease is crucial to patient-centered care. Patients with advanced chronic kidney disease are often faced with complex decision-making (including dialysis access planning and modality choice) in the setting of poor health and functional status which could impact quality of life at dialysis initiation.[24,25] Specifically, we demonstrated an appreciable difference in baseline quality of life between in-center and home modality incident patients, which remained stable over time if there was no change in modality. Our findings differ from previous longitudinal studies which have shown changes in certain aspects of HRQoL over time for patients who remain on the same dialysis modality.[12,15]

Table 6.2 Changes in HRQOL over time.[*,¶,¥]

	All (n=5114)			In-center to In-center (n=4179)			Home to home (n=814)			In-center to home (n=55)			Home to in-center (n=66)		
KDQOL subscales	Period 1	Period 2	Delta	Period 1	Period 2	Delta	Period 1	Period 2	Delta	Period 1	Period 2	Delta	Period 1	Period 2	Delta
PCS	38.6 (10.4)	38.7 (10.7)	0.4%	38 (10.3)	38.4 (10.7)	1.1%	41.1 (10.5)	40.2 (10.6)	-2.2%	38.5 (9.9)	38.5 (10.1)	0.1%	41.7 (10.4)	38 (10.6)	-8.9%*
MCS	51.7 (10)	52 (9.9)	0.5%	51.8 (10)	52 (9.9)	0.4%	51.5 (9.7)	52.1 (9.8)	1.2%	51.1 (9.9)	49.1 (9.8)	-3.9%	50.4 (10.2)	50.8 (9.9)	0.8%
SPS	81.3 (14.1)	80.7 (14.3)	-0.4%	80.7 (14.2)	80.4 (14.4)	-0.3%	82.8 (13.2)	81.6 (13.8)	-1.4%	78.4 (15)	80.2 (12.7)	2.2%	81.3 (15.4)	82.6 (13.3)	1.6%
BKD	54 (28)	54.6 (28.5)	1.0%	53.3 (28)	53.8 (28.6)	1.0%	58 (27.7)	58.4 (27.8)	0.6%	49.2 (30.9)	56.1 (29.1)	14.1%	57.1 (26.7)	53.5 (27.6)	-6.3%
EKD	77.2 (19.8)	77.6 (19.8)	0.5%	76.7 (20.1)	77.2 (20.1)	0.6%	79.9 (17.6)	79.8 (17.8)	-0.1%	71.4 (22.8)	76.9 (19.6)	7.8%	76.9 (19.2)	77.9 (19)	1.3%

Continuous variables are presented as mean (± standard deviation); [*] $p<0.05$ represents change in mean scores between Period 1 and Period 2; [¶]Period 1=Day 0 to 120 days after dialysis initiation, Period 2=Day 365 to 485 after dialysis initiation; [¥]KDQOL=Kidney Disease Quality of Life, PCS=Physical Component Summary, MCS=Mental Component Summary, SPS=Symptom/Problems, BKD=Burden of Kidney Disease, EKD=Effects of Kidney Disease (EKD).

However, one recent study prospectively investigated health and functioning status (via self-reported health status and the presence of bothersome symptoms via the KDQOL-SF) among older patients receiving chronic dialysis.[17] Patients who received home hemodialysis or peritoneal dialysis were each independently found to have decreased risk for low health status compared to those who dialyzed within clinics after 12 months of treatment. Most patients in the study were noted to have stable or improved health status over time. After dialysis initiation, patients may improve clinically and adapt to lifestyle changes which may result in similar quality of life. Furthermore, compared to in-center dialysis patients, patients on home dialysis modalities may have higher HRQoL because they feel less disruptions from their disease and are less likely to perceive themselves in a patient role.[26] Regardless of dialysis modality, closely assessing physical and mental function and effectively managing symptom burden is key to preserving patients' HRQoL over time.[27]

Although few studies have investigated the association of patient well-being with changes in ESRD treatment,[28,29] we noted that certain aspects of quality of life changed over time depending on dialysis modality. In particular, the BKD subscale score (which addresses the burden of kidney disease on life activities, relationships etc.) appeared to increase when patients switched from in-center dialysis to home modalities and decreased when they changed from home modalities to in-center dialysis. In-center dialysis patients who switched to home modalities also appeared to be bothered less by the effects of kidney disease on their daily life as evidenced by higher EKD subscale scores. A recent systematic review of qualitative studies of dialysis patients and their caregivers noted that many viewed home hemodialysis as a modality that provides independence, flexibility, and strengthened relationships.[30] These feelings may also extend to peritoneal dialysis patients although the reverse may be true specifically for elderly and frail patients who have greater physical and cognitive dysfunction.[31,32]

Additionally, we noted a significant decrease in the PCS subscale score when patients switched from home modalities to in-center dialysis. Patients who transition from home modalities to in-center dialysis may do so because of ultrafiltration failure, infection, or access-related problems which could ultimately contribute to progressive physical limitations after loss of residual renal function.[33-35] Home modality patients may also choose to switch to in-center dialysis after suffering from isolation or emotional distress if they do not have adequate social support.[36-38] Given these stipulations, providers should clearly delineate the potential positive and negative health status changes that could potentially occur when patients switch dialysis modalities. Engaging in shared dialysis decision-making where the specifics of each dialysis modality are reviewed can help patient reconcile their unique strengths and weaknesses with treatment objectives.[39-41]

While our study has several strengths, there are some limitations. There may have been unmeasured confounders that introduced bias into the study. Although we confirmed different patterns of HRQoL by dialysis modality, we could not infer causality due to the

observational nature of the study. Also, we were unable to ascertain patient preferences for dialysis modality, and therefore could not deduce whether there was a "mismatch" of modality with patient lifestyle. We acknowledge that matching more home modality to in-center dialysis patients would have been most ideal if there had been a larger study population. Lastly, as we grouped home hemodialysis with peritoneal dialysis patients based on a desire to focus on modality setting, we were unable to assess individual patterns of HRQoL as well as transfers between the two modalities and any possible subsequent effects on HRQoL.

In conclusion, different patterns of HRQoL at the time of initiation and over time vary by dialysis modality. Home modality patients appear to have higher HRQoL compared to in-center patients and less physical functioning when switching to in-center dialysis over time. More research is needed to determine the significance of patients' preferences for dialysis modality on HRQoL over time. However, providers and patients should be mindful of possible quality of life changes that may occur when transitioning to a different dialysis modality to ultimately optimize patients' livelihood and dialysis experiences.

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Chapter 7

General discussion

General discussion

The major aim of this thesis is to describe and highlight key clinical and laboratory parameters at the time of transition to dialysis start. The transition from pre-dialysis chronic kidney disease (CKD) to early dialysis treatment is a complex time associated with increased morbidity and mortality.[1-3] Late stage CKD is inherently a time of deterioration in renal function with changes in hormones impacting red blood cell neogenesis and calcium and phosphorus metabolism. Progressive loss of kidney function also results in sodium and water retention and signs and symptoms of volume expansion. CKD is an independent risk factor for cardiovascular disease, with a multidimensional origin including hypertension, volume expansion, abnormal bone and mineral metabolism as well as inflammation and oxidative stress.[4-6]

At the start of dialysis these CKD physiologic changes are influenced by the renal replacement therapy (RRT) that manipulates fluid volume, sodium delivery, and calcium and phosphorus levels and exposes patients to artificial catheters and membranes that may contribute to inflammation and infection risk.[7] Hemodialysis (HD) treatment may cause cardiovascular instability affecting blood pressure (BP) and tissue and organ perfusion.[8-10]

This thesis focuses on mortality risk factors in the domains of nutrition, inflammation, bone and mineral metabolism, and cardiovascular parameters. Two unique datasets enable examination of these key parameters in the months before dialysis start and in the early, high mortality period after dialysis start: The Fresenius Medical Care North America (FMCNA) database and the Fresenius Medical Care-CKD Registry. The FMCNA database includes laboratory and dialysis treatment data for over 43% of the current United States (U.S.) outpatient dialysis population. The Fresenius Medical Care-CKD Registry includes data for over 500,000 patients geographically dispersed in the U.S. with CKD or end stage renal disease (ESRD) who receive care from nephrology practices utilizing a nephrology-focused electronic health record (EHR). Data elements including demographics, vital signs, lab results, and estimated glomerular filtration rate (eGFR) (calculated using the CKD-EPI and/or MDRD4 equation) are placed in the CKD registry.

The study of key clinical and laboratory parameters may lead to the recognition of clinical patterns associated with adverse patient outcomes around the time of dialysis transition. This may create opportunity for changes in clinical care that improve CKD patient outcome trajectories. Such data may lead to development of predictive models identifying CKD patients at increased risk for adverse outcomes at the time of dialysis transition.

The first chapters of this thesis examine clinical parameters associated with incident dialysis mortality and “optimal” dialysis start. The final two chapters examine factors associated with stable dialysis transition using a home modality and the impact on quality of life (QOL).

In **Chapter 2** we discuss systolic blood pressure (SBP) as an extensively studied mortality risk factor in the general population, in CKD, and in ESRD. BP guidelines in the general population and in CKD pre-dialysis recommend lowering BP to reduce cardiovascular risk. However, some studies suggest that ESRD is associated with a "reverse epidemiology" such that patients with low or normal BP have increased mortality risk compared with patients who have "high" BP.[11,12] Other studies report a "U-shaped" curve in ESRD such that low (SBP <110 mmHg) and high (SBP ≥180 mm Hg) are associated with increased cardiovascular mortality.[13] Additional studies suggest increased mortality for ESRD patients who have pre-dialysis SBP that is ≤140 mmHg.[11,12]
In addition to increased cardiovascular risk with low and "normal" SBP in ESRD patients, BP variability (BPV) is associated with increased mortality. BPV during dialysis treatment (intradialytic BPV) is associated with adverse cardiovascular outcomes.[14] Visit-to-visit BP variability, e.g. based on the standard deviation of BP across dialysis treatment visits is also associated with increased mortality.[15,16] In a large observational cohort, patients with either an increasing or decreasing BP trend over 1 year of dialysis had decreased survival in the following year.[17]
Few BP studies in ESRD examine the relationship between BP and outcomes at the time of transition from pre-dialysis CKD to dialysis start and during the first months of dialysis treatment. Most studies either do not have access to BP data during the first 90 days of treatment or exclude patients in the high mortality incident dialysis period. Prior studies also focus on long-term outcomes related to absolute BP or BPV. The FMCNA database supports examination of pre- hemodialysis SBP (preSBP), systolic BP measured just prior to the start of each dialysis treatment, captured from the first day of dialysis throughout the first dialysis year and the association with short-term mortality in the following week.
Study results in **Chapter 2**, confirms and adds to the literature that in a national U.S. dialysis population with data captured in the FMCNA database the highest overall patient mortality is at week 2 after HD start. Starting with the first week of HD we studied the relation between low preSBP (<110 mmHg) and mortality in the following week. We examine preSBP levels including the percent of prior weeks with low preSBP and "current" week low preSBP, as well as BPV, defined as the percent of prior weeks switching between low and high preSBP. While all 3 aspects of low preSBP are associated with increased short-term mortality, "current" week low preSBP is most consistently associated with adverse short-term outcomes and this remains true throughout the first year of dialysis.
This study describes the increased risk associated with each week of low preSBP from the first week of dialysis treatment. Our study confirms previous findings that ESRD patients with preSBP <110 mmHg are at higher mortality risk, but adds to the literature by showing that this risk is present in the very short term. BP is routinely measured at the start of every dialysis treatment and it is a visible parameter for all clinicians caring for patients on HD. This study highlights the importance of evaluating absolute preSBP

measurements at the start of every HD treatment increasing awareness of the risk for HD patients who have or progress to low preSBP levels.

This observational study cannot confer causality for low and normal preSBP and mortality, but it does highlight the association of this potentially modifiable risk factor. Recognition of increased risk may prompt clinicians to closely evaluate dialysis patients with preSBP <110 mmHg for conditions contributing to low BP and to modify care and treatment to increase preSBP. In particular, recent studies suggest that low BP in ESRD may impair cerebral or cardiac perfusion resulting in cardiac stunning or chronic cerebral ischemia and poor patient outcomes.[18] Low BP and BPV may also reflect underlying low cardiac output.[14,19] Recent data show that volume status may have a major effect on the relationship between BP and mortality in dialysis patients, as low SBP (defined as pre-HD SBP <110 mmHg) in combination with fluid depletion or fluid overload was associated with increased mortality, whereas in euvolemic patients low SBP was associated with improved outcomes.[20]

Our study suggests that preSBP <110 mmHg should alert clinicians to the need for timely clinical evaluation since mortality risk is short-term. Rapid evaluation of fluid status and possibly cardiac status appears mandatory in this group. Future studies are needed to further elucidate clinical features and parameters of patients with preSBP <110 mmHg during the first weeks of dialysis to identify causal factors for mortality risk.

Chapter 3 provides a closer look at the transition from late stage CKD to dialysis start which is a critical period associated with the highest annualized dialysis mortality.[2,7] Modifiable clinical factors in pre-dialysis CKD impact patient outcomes after the transition to dialysis start.[21,22] It is known that the quality and quantity of CKD care and permanent access preparation at the time of dialysis start influence early dialysis outcomes such that CKD care that results in an “optimal” dialysis start is associated with improved dialysis patient outcomes.[23-25]

Adverse physiologic trends impacting outcomes in early or incident dialysis are present in the months before dialysis start. Specifically malnutrition, inflammation, bone and mineral metabolism and cardiovascular disease are key physiological domains contributing to early dialysis patient outcomes.[2] Previous studies have identified patient characteristics associated with early dialysis mortality including low albumin, abnormal phosphorus, abnormal hemoglobin, cardiovascular disease and increased inflammatory states.[26] These factors are associated with increased mortality in the first 120 days of dialysis and cardiovascular events are the leading cause of mortality throughout the first year of dialysis in the U.S.[26]

It is hard to study the association between pre-dialysis parameters and outcomes after dialysis start in the U.S. since pre- and post-dialysis clinical and laboratory data are not stored in the same database. The Fresenius Medical Care (FMC)-CKD Registry contains deidentified, continuous clinical data for over 500,000 U.S. CKD patients some of whom transition to dialysis treatment. In the study outlined in **Chapter 3** FMC-CKD Registry data is analyzed for patients with at least 12 months of CKD care before dialysis start in

order to study clinical and laboratory trajectories for patients who did and did not survive the first year of dialysis.

For non-survivors SBP declines more rapidly in the months before dialysis start compared to patients who survive the first dialysis year. Non-survivors also have a more significant decline in albumin and serum sodium as markers of nutrition and inflammation in the months before dialysis start. In addition, white blood cell (WBC) count is higher in the CKD pre-dialysis months for non-survivors and body weight is consistently lower. During the 12 months prior to dialysis start non-survivors have a higher estimated eGFR initially and a more rapid eGFR decline consistent with a steeper slope of renal function decline in the months before dialysis transition. This steeper decline in renal function may be associated with underlying severity of inflammation and cardiovascular disease as a marker for mortality risk, although this needs to be confirmed in future studies.

Chapter 3 study results suggest that key clinical and laboratory parameters associated with increased mortality in the first dialysis year begin to diverge for survivors and non-survivors in the months before dialysis transition. Additional studies of specific inflammatory markers and the association with chronic fluid overload and uremic toxins in CKD are needed. Our study also suggests that more rapid eGFR decline is associated with early dialysis mortality, but this parameter is not routinely examined as a risk factor for adverse dialysis outcomes. Future studies examining CKD care associated with optimal dialysis outcomes should consider trajectories of key clinical parameters in late stage CKD including the slope of eGFR decline.

While our data support examining trajectories of CKD clinical parameters before the start of RRT it is unclear if these clinical trajectories can be changed to improve patient outcomes. More research is needed to understand the cause and role of inflammation and to determine if cardiovascular risk factors can be altered. If modifiable risk factors are identified, then the months prior to dialysis transition represent a “window of opportunity” to reduce early dialysis mortality.

Some pre-dialysis factors that impact early dialysis outcomes may be patient-specific such as inflammation, cardiovascular disease and nutrition, but other factors impacting dialysis outcomes are related to CKD clinical care as we examine in **Chapter 4**. Early referral to nephrology is recommended to improve CKD care and dialysis start, however, it has been shown that duration of nephrology practice care alone does not ensure an “optimal dialysis start”.[27] Studies show that dialysis treatment options education during late stage CKD decreases early dialysis mortality[28,29] and multidisciplinary team care that includes CKD education and permanent dialysis access placement in CKD clinics improves dialysis outcomes.[21,22,30] CKD programs that increase the likelihood of an “optimal dialysis start” decrease early dialysis mortality.[24]

Chapter 4 describes a case-management CKD intervention to improve the likelihood of an “optimal start” transition to dialysis treatment. This intervention uses clinical data to identify late-stage CKD patients within a nephrology practice and to track delivery of

guideline-based CKD care. The intervention includes case-managers using weekly and monthly data to coordinate delivery of CKD and treatment options education, to monitor CKD progression, to support patients in making treatment decisions, and to improve the likelihood that patients have an "optimal start" to dialysis with use of a permanent HD access or use of PD. In addition, our study confirms that delivering recommended late stage CKD care and having a planned start to dialysis results in fewer hospital days and lower mortality in the first 120 days of dialysis.

Results in **Chapter 4** suggest that weekly late stage CKD patient population tracking coupled with case management can improve the likelihood of a stable transition to dialysis start. This study supports previous research suggesting that an "optimal start" improves early dialysis outcomes including reducing mortality during this critical transition time. While this study supports previous findings that multi-disciplinary CKD care improves dialysis outcomes, but the impact of specific interventions is still unclear. More research is needed to determine which interventions matter most. Some interventions of the renal care coordinator (RCC) program result in improved clinical care that addresses known CKD and dialysis transition risk factors including nutrition and mineral metabolism care through improved patient education and support for medication management. In addition, starting dialysis with a permanent access is associated with reduced risk of infection, inflammation, and mortality compared to use of a central venous catheter. Other interventions support psychosocial issues such as arranging appointments and transportation, so it is unknown if physiologic or psychosocial interventions impact early dialysis outcomes most.

Future work with predictive models to identify patients most likely to progress from late stage CKD to ESRD is needed. In this study, the RCC intervention was delivered to all CKD patients with an eGFR <30 ml/min, but many of these patients will never progress to ESRD. The ability to identify patients at risk of advancing to ESRD within the next 6-12 months would improve efficiency of delivering interventions to the right patients at the right time. Predictive models for CKD progression and onset of ESRD would also improve the timing for placement of a permanent dialysis access. In addition, identifying patients at risk of ESRD would reduce the anxiety and additional intervention exposure for patients who are not at risk for ESRD within the next year.

For patients at risk of ESRD, additional tools are needed to identify best treatment options. In the RCC intervention, patients are provided treatment options education to support decisions about which dialysis treatment modality they prefer. More data is needed to help patients identify not only a preferred modality, but also the modality that is likely to provide the best patient outcome. Risk models and predictive analytics would improve delivery of the right CKD interventions to the right patients at the right time.

The study in **Chapter 5** examines CKD trajectories for peritoneal dialysis (PD) versus HD starters. HD and PD differ in technical aspects of dialysis and ultrafiltration, site of care delivery, and in social aspects of self-care. PD utilizes the natural semi-permeable

membrane properties of the peritoneal cavity lining and peritoneal dialysate is infused either manually or with mechanical assistance into the peritoneal cavity. Compared to HD patients PD patients experience differences in some clinical parameters such as albumin (Alb) due to characteristics of the peritoneal membrane compared to synthetic HD dialyzer membranes.[31] PD is a continuous therapy with less hemodynamic and cardiovascular impact compared to HD, but PD patients are exposed to an indwelling catheter and peritoneal dialysate that may be associated with increased inflammation.[32-35]

Some studies suggest that patients starting dialysis on PD have better outcomes than patients starting HD.[36-38] Not all studies confirm this finding and some studies suggest that case-mix differences in patients who start PD versus HD cause a difference in dialysis outcomes.[39-41] Case-mix differences for PD versus HD starters are hard to identify since, as we have shown,[42] CKD factors before dialysis start influence early dialysis outcomes and most studies examine PD and HD starter differences only from the first day of dialysis. Identifying different CKD trajectories for PD versus HD starters may be relevant to early dialysis outcomes.

Studies of outcomes for PD versus HD starters are complicated by the differences in treatment technique. Treatment characteristics including dialysis membranes, vascular and PD accesses, and continuous versus intermittent treatment affect physiologic risk domains including inflammation, nutrition, mineral metabolism and cardiovascular disease. In **Chapter 5** the FMC-CKD Registry database is used to examine CKD trajectories through the transition to dialysis start and first year of dialysis for PD versus HD starters.

Results in **Chapter 5** show that at 12 months before dialysis start, PD and HD starters have similar findings for key clinical and laboratory parameters in cardiovascular, nutritional, inflammatory and mineral metabolism domains. In the months before dialysis start HD starters experience a more rapid eGFR decline. HD starters concomitantly have a greater decline in hemoglobin and rise in phosphorus. Consistent with fluid overload in CKD, HD starters tend to have a steeper rise in SBP and body weight compared to PD starters. In the months after dialysis start HD starters experience a steeper decline in SBP, body weight, and phosphorus compared to PD starters who have more gradual changes. Albumin, a marker of inflammation and nutrition, remains lower for PD starters after dialysis start compared to HD starters.

Chapter 5 data uniquely demonstrates differences that begin in late stage CKD for PD starters versus HD starters. These differences include key clinical parameters known to be associated with adverse early dialysis outcomes. In particular, HD starters have a steeper decline in renal function in the year before dialysis start which may be relevant for early dialysis survival. Patients who decline more rapidly may not be as well prepared for an “optimal dialysis start”. Also, more rapid decline may reflect worse underlying disease, including cardiovascular disease.

This study also suggests that PD starters may experience ongoing inflammation after dialysis start. More research is needed to understand possible pre-inflammatory attributes of PD catheters and PD fluid biocompatibility. Given recent revelations regarding hemodynamic changes causing cardiac stunning and cerebrovascular ischemia[7 in HD, the differences in SBP and body weight slopes in HD starters compared to PD starters should be further studied.

Patient-Reported Outcomes Measures (PROMs) can be captured in CKD patients using instruments such as the Kidney Disease Quality of Life – 36 (KDQOL-36) or KDQOL – short form (KDQOL-SF).[43] Patient symptoms including fatigue, pain, mobility, sleep quality, and mood relate to physical and mental component scores and reflect the burden of disease.[43] Improving patient communication about symptoms provides an opportunity to change patient care and improve patient outcomes.[43]

Patient perceptions of health and quality of life (QOL) as measured by the KDQOL - SF is the research subject in **Chapter 6**. In dialysis, health related QOL (HRQOL) is associated with adverse outcomes including poorer treatment adherence, increased hospitalization, and higher mortality.[44-46] Longitudinal studies of HRQOL for PD versus HD patients have been done, but sample sizes have been small and follow-up times short. The **Chapter 6** study examines HRQOL for a large cohort of home therapy patients starting either on home HD or PD compared to incenter HD starters in the early dialysis period. We evaluate changes in HRQOL after the first year of dialysis for patients who remain on their starting treatment modality versus those who switch from incenter to home treatment and vice versa.

Results in **Chapter 6** show that incenter HD patients have lower mean KDQOL scores compared to home therapy patients in the first 120 days of dialysis. For incenter HD patients, the Burden of Kidney Disease KDQOL subscale score was clinically and statistically poorer compared to home therapy patients. This outcome may reflect a selection bias for patients who are healthier and choose home therapies versus patients who do not have that option. However, as below, our study identifies an improvement in KDQOL associated with changing from incenter HD to a home therapy suggesting that the home setting with greater patient autonomy and flexibility may itself improve patient perceptions of QOL.

For patients who remained on their starting treatment modality, little change was seen in KDQOL scores over the first year of dialysis. However, these data suggest that switching treatment modality during the first year does impact KDQOL scores: Patients who switch from incenter to home have improvement in some KDQOL subscale scores and patients who change from home to incenter treatment have some subscale score changes that suggest a decline in QOL.

In late stage CKD and at the time of dialysis start, patients make treatment modality decisions based on a variety of factors. HRQOL has been shown to be associated with patient outcomes including nutritional parameters such as albumin as well as hospitalization and mortality.[47] Although HRQOL relates to patient outcomes, especially

in the physical domains, little is known about the differences in HRQOL at dialysis start and during the first year of treatment based on starting modality choices. Our study suggests that home therapy is associated with slightly better mean KDQOL scores at dialysis start and throughout the first dialysis year for patients who remain on their starting modality. However, it is not clear whether this would affect patient outcomes.
Switching treatment modality during the first year appears to change KDQOL scores. Switching from home to incenter treatment appears to adversely impact some aspects of QOL. These data suggest that clinicians caring for patients who switch modalities during the first year should be aware of the possible impact on patient perceptions of QOL and the related impact on clinical outcomes possibly including hospitalization and mortality. Our data are not sufficient to study subgroups of patients to determine if this is true for all patients. For example, elderly, frail patients may be impacted differently by modality and switching compared to younger, healthier patients.
In summary, this thesis focuses on late stage CKD, the transition to dialysis start, and the early dialysis period. We examine the impact of clinical and laboratory parameters in known risk domains for pre-dialysis and post-dialysis start trajectories and the association with early dialysis outcomes. We show that delivery of CKD interventions improves dialysis start and early dialysis outcomes. Access to a unique CKD transition and early dialysis databases enabled study of HD versus PD starters and outcomes including QOL. These studies highlight the impact of pre-dialysis CKD care and clinical trajectories on outcomes after dialysis start. Improved understanding of key CKD characteristics provides an opportunity to improve early dialysis outcomes.
Previously, studies examining outcomes in the first year of dialysis considered clinical parameters only after dialysis start or even after the incident dialysis period. The time of transition to dialysis start should be considered a continuation of the pre-dialysis CKD course. Future studies of early dialysis patient outcomes should include analysis of clinical and laboratory parameters in late stage CKD which influence dialysis start and mortality. In addition, specific CKD care including clinical interventions and patient QOL should be considered as dialysis outcome risk factors.

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Summary

Summary

This thesis examines clinical and laboratory parameters and clinical interventions through late stage chronic kidney disease (CKD) and the transition to dialysis start that impact outcomes in the early dialysis period. This research utilizes a unique CKD dataset that includes continuous pre- and post-dialysis start data. In this research key parameters and interventions known to be associated with patient outcomes including cardiovascular, nutritional, mineral metabolism, and inflammatory parameters as well as quality of life (QOL), educational, and case management measures and interventions were explored.

In **Chapter 2** the examination of presystolic blood pressure (preSBP) and ultra-short-term mortality yielded insights into the increased risk of short-term mortality for low preSBP from the first day of dialysis and throughout the first dialysis year. This data highlights the need for dialysis clinicians to consider timely additional assessments for dialysis patients with low and low-normal preSBP especially in the early dialysis period.

In **Chapter 3** key clinical parameters including BP, albumin, and white blood cell (WBC) count as indicators of cardiovascular, nutrition, and inflammation were assessed in late stage CKD through the transition to dialysis start. These clinical parameters were shown to diverge before dialysis start for patients who survive versus do not survive the early months of dialysis. Such findings suggest that it may be possible to identify patients at risk for poor early dialysis outcomes and provide additional care, support, or interventions in the months before dialysis start.

Chapter 4 reports an improved dialysis start for patients who receive specific interventions delivered in a case-management CKD program. This improved, optimal dialysis start including use of a home therapy and a permanent access is associated with better dialysis outcomes demonstrating the impact of late stage CKD care in early dialysis outcomes.

Chapter 5 compares late stage CKD clinical parameters throughout the time of transition to dialysis start for peritoneal dialysis (PD) versus hemodialysis (HD) starters. Some previous research suggests that PD starters have better early dialysis outcomes compared to HD starters, but PD versus HD case mix comparison traditionally only includes data from the early dialysis period. Our data suggest that key parameters associated with the rate of CKD progression, nutrition, inflammation, and cardiovascular stability differ in the months prior to dialysis start for PD versus HD starters. Future research in early dialysis outcomes for PD versus HD starters may need to account for pre-dialysis start variability.

Chapter 6 highlights the impact on QOL of switching from HD to PD or vice versa during the first year of dialysis. QOL as measured by the Kidney Disease Quality of Life (KDQOL) instrument is known to be associated with clinical outcomes, yet no recommendation currently exists for QOL assessment or interventions to improve QOL at the time of switching from PD to HD or vice versa which may be of particular importance during the early dialysis period.

Valorization

Valorization

The time of transition from pre-dialysis chronic kidney disease (CKD) to dialysis start is a critical period associated with the highest annualized mortality for end stage renal disease (ESRD) patients. As documented by the United States Renal Data System, the time of transition to dialysis start is also costly to the healthcare system. The research documented in this thesis explores how trends in laboratory and clinical parameters in the pre-dialysis and early dialysis periods may impact patient outcomes and modality at the time of transition to dialysis. It further provides insight into some interventions that can be implemented to improve patient outcomes during this critical period.

The dialysis transition time is difficult to study in the U.S. in part because the legacy healthcare delivery pattern and current electronic health record systems (EHRs) segregate pre-dialysis CKD care from care delivered after day 1 of dialysis treatment. Pre-dialysis CKD patients receive care in the nephrology practice with clinical data collection in the practice EHR. On day 1 of dialysis treatment, the dialysis facility multidisciplinary team assumes the majority of the clinical care of the patient and this care is documented in the dialysis organization EHR. The Fresenius Medical Care – CKD Registry is a rare database yielding continuous data through the dialysis start transition.

The research included in this thesis and other data suggest that events during late stage CKD impact dialysis start and early dialysis outcomes. Particularly, studies have demonstrated that nephrology practice visits and CKD education in the year prior to dialysis start improve the likelihood of an optimal dialysis initiation and lower early dialysis mortality. As shown in our study, case managers with good population management tools and individualized patient support can improve the transition to dialysis. This case management model is resource intensive and not scalable in the U.S., so more research is needed to develop ways to efficiently deliver the right care to the right patient at the right time. These tools and processes will likely need to include telehealth, data-driven personalized algorithms, and online resources.

Data is critical to developing predictive models and insights that help match patients with the care they need at the right time. The development of real-time continuous clinical data repositories for the entire CKD care continuum from early CKD stages through the initiation of treatment for ESRD is needed. Such databases would support ongoing research and advance predictive and prescriptive analytics.

The transition to dialysis start needs to become a smooth, stable hand off from a nephrology practice setting to a dialysis treatment setting. More overlap time in clinical care between the CKD and ESRD care teams would be helpful. Pre-dialysis CKD clinical care teams should be held accountable for clinical quality goals that reflect a stable and successful dialysis start and early dialysis transition. In the U.S., payer reimbursement for optimal dialysis start and safe transition to ESRD care for both nephrology and surgical staff preparing patients for dialysis transition may provide incentives for improvement in outcomes.

In addition, more attention to patient and caregiver perceptions of quality of life is needed. In the U.S. today patients may not receive a first quality of life survey for up to 90 days after the first day of dialysis. This may delay clinical staff recognition of patient depression or treatment burdens. With peak mortality in the first 2 weeks of dialysis, the first days of dialysis should be viewed as a time of intensive assessment and support by the dialysis clinical team. This is also a good time for the nephrology practice clinical team with established patient relationships to be included in the clinical transition care team. Legacy reimbursement systems in the U.S. have been barriers to coordinating and overlapping pre-dialysis CKD and ESRD dialysis clinical care.

This research shines a light on this critical transition period for CKD patients. Future success will be easily measured by elimination of the steep rise in patient mortality and healthcare costs in the early weeks after the transition to dialysis start. New and better advanced analytical methods, such as predictive models, may help identify patients at high risk for unstable transition even before day 1 of the transition to dialysis begins.

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Acknowledgments/dankwoord

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This thesis and research would not have been possible without the daily support and contribution of Dr. Len Usvyat. My PhD ambitions are tied from the beginning with having been a guest at Len's PhD oral defense and celebration. Some weeks Len has been in my office daily helping me work through data analysis and manuscript revisions. He has traveled with me through Europe and the eastern seaboard of the U.S. to work through research ideas, data results, manuscript development, and draft revisions. On my behalf he has worked nights and weekends to solve data problems and he has helped coordinate resources from around the world to support this

research. He has been my teacher for crash courses in statistics and he has helped me produce tables, charts, graphs, and pictures to fill the manuscripts that compose this thesis. He is the backbone of this work.

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adult lives they care for me and provide daily examples to me about how to do meaningful work and care for others. They each share their lives with smart and generous partners, Christopher and Alexandra, and they all give of themselves everyday to make the world a better place. They not only care for each other, but take care of parents, grandparents, extended family, animals, clients, and communities to make the world a more loving, generous and better place. They have cheered me on and celebrate my success as a PhD candidate.

To my husband, Frank, I thank you for every day of our shared home and work life. As my soulmate you have influenced and supported all my personal and work choices and opportunities. You are my sounding board for learning, knowing, and being. Thank you for giving me support, time, resources, freedom, encouragement, and inspiration to complete this PhD journey. Thank you for helping to weave our home and work life together to make each day whole. All my love goes to you and our beautiful family.

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Curriculum Vitae

Curriculum Vitae

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Education

9/1976-6/1980	B.A. - Vanderbilt University (Chemistry)
9/1980-6/1984	M.D. – University of North Carolina

Postdoctoral training

6/1984-7/1987	Internship and Residency (Internal Medicine)
	UNC Hospitals
7/1987-7/1989	Fellowship (Nephrology)
	UNC Hospitals
1/2014 – present	PhD candidate, Maastricht University

Board certification

1987	Diplomat of the American Board of Internal Medicine
1990	Nephrology Certification
2000	Nephrology Re-certification

Employment

7/1989- 2/2008	Nephrologist, Danville Urologic Clinic Danville, VA
2/2008-12/2010	Maddux Consulting
	Contractual agreement with FMCNA Medical Office
1/2011 - present	Fresenius Medical Care North America
	Vice President of Kidney Disease Initiatives

Professional memberships

Fellow, American College of Physicians
Renal Physicians Association
American Society of Nephrology

Honors and awards

1976-1980	Harold Sterling Vanderbilt Scholar
	Vanderbilt University
1980	Phi Beta Kappa

1980 Young Alumni Member of the Vanderbilt University Board of Trust

Community activities

Past Board Member and Past President of the Dan River Region Community Foundation
Board Member, Epiphany Episcopal School
Past President, Danville Soccer Club

Professional activities

Acumen Physician Solutions – Monthly blog contributor
Co-Founder, Health IT Services Group, LLC
Co-Founder, Gamewood, Inc.
Co-Founder, Voice Expeditions featuring the Nephrology Oral History Project
Past Director of the VA Chapter of the ACP "Internists as Artists" program

Publications

Voice Expeditions Website: The Nephrology Oral History Project
EVINCE Technology Column "Bit by Bit"
This Side of Doctoring, "Spiderlings" essay

Articles

"A History of Leadership in Nephrology: Perspectives from Seasoned Leaders", Dugan W. Maddux. *ACKD in press*

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"Mycobacterium chelonei facial abscess: case presentation and review of cutaneous infections due to Runyon Group IV organisms. Hamrick, Maddux, Lowry, Taylor, Henderson, Pillsbury. *Ped Inf Dis*, 3(4):335, 1994